

Should scientists be re-auditioned?

In general artists live by their wits and survive through being productive. If they are painters they must continue to paint and sell. If they are musical performers they must continue to keep a high standard of performance—in an orchestra that will mean a regular re-audition. It is a ruthless existence and yet one about which few of those involved in it, or even those who were once involved in it and have been left behind, feel bitter. There is often a feeling that the state should support an orchestra, an art gallery, a theatre, but rarely do individual creative or performing artists reckon that the state owes them a living. Indeed it is thought quite natural that they should move into teaching when they find their other abilities waning, without in any sense regarding teaching as an inferior profession.

What is it about scientists and the scientific profession which makes the idea of something even remotely similar amongst themselves unthinkable? In certain trades and professions it is possible to point to an accumulation of worldly goods which prevents any major changes in course—a taxi-cab, a workbench and tools, dental equipment. In others, more experience makes for greater capability as time goes on. Politicians, priests, bartenders probably feel that way. But a scientist neither owns his tools (beyond a relatively few books and journals of current use to him) nor demonstrably improves with age, unless he be in the business of cataloguing or collecting. Why then should he dig in for life, as he is very prone to?

One reason, of course, is that it is a very pleasant life, involving lots of travel, and in terms of service many scientists are near to being self-employed without the financial responsibilities that self-employment involves. Another is that the outside world seems to offer a great deal less stability, if it offers anything at all. Yet another is that scientists often delude themselves that it is creditable to go on working on the same old problems, gradually chipping them away, when the very last thing that most scientific problems need is the attention of one man, often to the exclusion of others, for thirty to forty years.

The community of older scientists must inevitably continue to grow for the foreseeable future and at some time governments, industry and academe are bound to have to ask whether the ranks of an ageing workforce can be allowed to continue to swell. This question is indeed being faced now by many institutions, world-wide, which sprang up in response to immediate post-war defence needs. Academics can maybe justify themselves by increased teaching and administrative loads and a growing involvement in maintaining the standards of

the college wine cellar. Others have no such outlets unless they are specifically plucked out of 'science' and dropped into 'administration'; and this is said to be a move that few are allowed to make.

There is a case, then, for scientists to come up with some fairly concrete proposals on the employment of older members of the profession before the government or other large scale employers step in with their own schemes for thinning the ranks. And perhaps some sort of re-auditioning system should be discussed in conjunction, of necessity, with an extensive rethinking of the career structure of scientists. It is obviously pointless to urge or even force someone out of his laboratory without any guarantee that other jobs can be found which do not involve a humiliating change.

If at the present this is not so, then it is time that scientists as a community started talking seriously about their prospects. It is only depressing that in Britain at present there is not a suitable forum for this, although we suggest elsewhere in this issue (page 743) that the British Association ought to become a gathering of thoughtful scientists. Then ultimately it should be possible to approach the government with rather specific proposals that every year a substantial number of intelligent, well trained and experienced men would be available at ages between, say, 35 and 50 for redeployment—and what could be available within the public and educational sector? The answer would, of course, be nothing, but a start would have been made in asking important questions about skilled manpower. It is impossible to believe that in reality such men are unemployable when there is an apparent shortage of intellect all around.

Many scientists would, we believe, welcome the opportunity to use formal review points in their career, perhaps every five years between 35 and 50, to make a sideways step as a means of self-regeneration. In that way the audition could almost be a self-audition. But they should not expect jobs to be waiting for them unless they have done a lot of hard lobbying first.

A hundred years ago



ON Friday evening M. Flammarion, the French astronomer, started from La Villette gas-works, Paris, in a balloon called *Lumen*, at half-past seven, with a brisk breeze from the north-west. The balloon was under the guidance of M. Jules Godard, and M. Flammarion, who was married in the beginning of August, was on board with his young wife; he wishes to spend his *lune de miel* in Italy. Such a trip was proposed in the beginning of the century to the celebrated M^{me}. de Staël by the great philosopher, Saint-Simon; but the lady declined. The moon was full and bright.

From *Nature*, 10, 360, September 3, 1874.



international news

THE community of nations has gathered for the third time to develop a new order in the sea. What in 1967 started as a limited exercise to establish a regime for the seabed and the ocean floor beyond the limits of national jurisdiction, has developed into a formidable project whose objectives are to revise the whole philosophy of the law of the sea in an attempt to redress the balance between developing and developed countries. It is 15 years since the completion of the four 1958 Geneva Conventions which tried to establish rules for the use of the seas and now, after a very short interval, even their essential postulates are in question.

The old principle of the freedom of the seas which basically asserts that all States have equal rights to use the seas and which stood solid as a rock for more than 350 years is the object of serious attacks—the most dramatic change taking place is in the breadth of the coastal area over which various States claim sovereignty or jurisdiction; this may extend to 200 nautical miles (370 km) or to the outer edge of the continental rise if this feature goes beyond the 200 nautical miles. If this claim is accepted, more than 30 per cent of what today is high seas and which enjoys the freedom established in the 1958 Geneva Convention on the High Seas will come under the jurisdiction of coastal States—foreign vessels will have only the right of “innocent passage”. The other rights, including the one to conduct scientific research will disappear under this new concept.

The main battle at the Caracas Conference is being fought in the Second Committee where the right of coastal States to establish an exclusive “economic zone” or “patrimonial sea” beyond its territorial sea is under consideration. At the time of writing, about 20 days from the end of the Conference, there are the following tendencies on this matter:

(1) Territorial sea

- States which claim 12 nautical miles. The great majority of countries support this, but only if an economic zone of 200 nautical miles is accepted. This territorial sea of 12 miles, say the major maritime powers, may not impede transit through straits used for international navigation;

- States which claim 200 nautical miles; Brazil, Ecuador, Panama, Peru, Somalia, Uruguay.

(2) Economic zone or patrimonial sea

- States which claim an economic zone beyond the 12 miles’ territorial sea

Report from Caracas

extending to 200 nautical miles enjoying exclusive rights on exploration, exploitation and management of living and non-living resources; on prescribing standards for the preservation of the marine environment; and on the regulation of scientific research: Argentina, Australia, Canada, India, Kenya, Mexico, Tanzania, Venezuela and many others.

- States which accept 200 nautical miles economic zone but with certain conditions: (1) the coastal State will not necessarily have exclusive rights to living resources; that in order to ensure the full utilisation of living resources an obligation must be put on the coastal State to allow other States access to the resources which they do not utilise; (2) that the coastal State may enforce pollution standards agreed upon internationally but may not itself prescribe those standards unilaterally; (3) that the consent of a coastal State is not required to conduct scientific research once the vessels of other countries meet certain specified obligations.

(3) Definition and delimitation of continental shelf

The difference is between those States wishing to include the continental shelf in an economic zone of 200 nautical miles and those States like Argentina, Australia, Canada, which will prefer to go beyond 200 miles to the outer edge of the continental rise if this is larger than 200 miles.

(4) High seas and international seabed area

The need for a Seabed Authority is being accepted by the majority of States but they differ on the role to be assigned to such an Authority. A great number of developing States want to empower it with the management of living and non-living resources as well as the protection of the marine environment and regulation of scientific research. The great maritime countries want to endow the Seabed Authority with responsibility for the administration of the exploitation of the seabed resources only. The system of exploitation, conditions of exploitation, machinery, and economic implications of exploitation remain to be solved.

The specific problem of marine scientific research and transfer of tech-

nology is being dealt with in Committee III. Here the discussions have concentrated on the definitions and objectives of marine scientific research, and the conduct and promotion of marine scientific research, including the right to conduct, granting of consent, participation and obligation of coastal States, and the general conditions for the conduct of marine research.

It is generally accepted that the proper management of the marine environment and its resources depends upon knowledge of the sea—however, management-orientated research is generally considered to be applied in nature; consequently the developing countries feel very strongly about the need to regulate such research, not only in the economic zone but also in the international sea. They feel less strongly about pure scientific research; but it is very difficult, if not impossible, to distinguish between pure research and economic or military research.

The general tendency (particularly within the developing countries) is to regulate scientific research in the territorial sea and economic zone. Consent can be refused in the territorial sea but in the economic zone “shall not” or “may not” be withheld if some specified conditions are met. The stronger “shall not” is proposed by Ireland and “may not” by Mexico. These conditions are very similar to those recommended by the International Council of Scientific Unions (ICSU) in its statement on freedom of scientific research and also the conditions being met within the International Decade of Ocean Exploration of the Intergovernmental Oceanographic Commission.

The conditions to be met can be summarised as follows:

- (a) Participation by developing countries in all phases of the work (from planning to the final results). This condition is directly related to the problem of development and transfer of technology, about which developing countries feel strongly.
- (b) Collected data and samples, as well as written up results, be made available as soon as possible to the coastal State.
- (c) That the research is being conducted for peaceful purposes.

The present discussions seem to indicate that there is complete agreement on the need to establish a viable framework for the conduct of marine scientific research. □

Oil platform question still confused

by Eleanor Lawrence

THE British government has finally decided that some sort of planning policy is necessary to solve the vexed question of where in Scotland to build concrete gravity-type oil production platforms. But the statement may raise more problems than it solves.

Mr Eric Varley, Secretary of State for Energy, proposes that a limited number of future sites should be taken into public ownership in order to:

- maximise their use
- avoid proliferation of sites
- ensure only the minimum amount of infrastructure (such as roads and housing) is built
- make sites available in good time for the best platform designs
- enable strict control to be exercised over the development and eventual restoration of the sites.

But Mr Varley also emphasises that normal planning controls and procedures will not be by-passed, and in this his proposals differ from those of the last government which proposed to short-circuit planning procedures but not to acquire the land.

It is difficult to see how these two requirements will marry happily. On the same day that Mr Varley made his statement, the Secretary of State for Scotland, Mr Willie Ross, announced the results of the Drumbuie enquiry. This has ended in a victory for the National Trust and the villagers amongst others, since Mowlem/Taylor Woodrow's application to build Condeep concrete gravity platforms at Drumbuie, on one of the most beautiful parts of the north-west coast of Scotland, was turned down on environmental grounds after a lengthy public enquiry.

The result of the Drumbuie enquiry has both heartened and confused the environmentalists. Mr Ross said in his statement that he was not persuaded that the possible national gains depended solely on the Condeep design which Mowlem/Taylor Woodrow wished to build. This design can only be constructed at the very deep water sites in that area. The fact that the Drumbuie land is owned by the National Trust was also an important factor in the decision, since even if permission had been granted, parliamentary approval would have been needed. But Mr Ross also said that the official Reporter for the enquiry had examined five other sites nearby and had concluded that all were, or might be, suitable. There is already an application by Howard/Doris to build gravity platforms at Loch Kishorn further up the coast; this has been approved in principle by the local authority and objections are being con-

sidered by Mr Ross at the moment.

What confuses environmentalists is that development anywhere in the area will potentially be equally as destructive as at Drumbuie, since other sites under consideration (such as on the Crowlin Islands in the strait between Skye and the mainland) are even more remote from road and rail communications and are so near Drumbuie that the same social objections can also be made. Mr Ross has refused a public enquiry at Loch Kishorn on these very grounds—that the objections are so similar that they need not be debated publicly once again.

Mr Ross has also said that his criteria for choosing a suitable site are

- that it must have access to existing facilities
- that it can draw on an existing labour source
- that it can make use of existing infrastructure such as roads and services

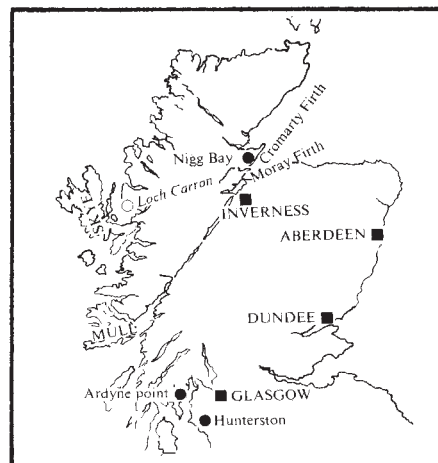
None of the Loch Carron area sites satisfies these criteria so the environmental groups opposing the Loch Kishorn application are hopeful.

But Mr Varley has put the Condeep platform design on his list of 'approved designs' for which he is willing to acquire sites. For his purposes, approved means most favoured by the oil companies. And the only place in Scotland that Condeep can be built is at one of the Loch Carron sites, which have exceptionally deep water close to a flat shore area.

For some time Condeep was thought to be the cheapest and best design for the deepwater oilfields but recent events have proved that this may not necessarily be so, and the image of Condeep as the saviour of the national economy is being challenged from several sides.

A spokesman for the Conservation Society said that as far as the Loch Carron area was concerned, Mr Varley's proposals were "irrelevant" because the society feels that the Condeep platforms are unnecessary. They point to the very successful French design which McAlpine is building at Ardyne Point on the Clyde near Glasgow. This Seatank platform can operate in 600 feet of water but unlike the Condeep does not need very deep water close to the building site, and can be towed some distance for final assembly.

Another blow to claims that the Condeep design is uniquely suitable for deepwater operations came when Shell ordered an Andoc concrete gravity platform for its deepest water site in the Dunlin field and Signal Oil chose a steel design for its Thistle field because seabed conditions proved unsuitable for gravity platforms. Diffi-



culties have also been experienced during the construction of Condeep platforms, at the time when the base is submerged. It was found that when submerged, one of the hollow base cells cracked under the water pressure and the design had to be modified so that the cells could be filled with concrete to overcome this.

Mr Varley's proposals could prove useful, however, in preserving the continuity of work at east coast sites. McDermott at Ardesier near Inverness has no more orders and the workforce faces redundancy as soon as present work is finished in a relatively short time. Mr Varley may find himself faced with the need to use his intended powers of restoration of the site and redeployment of the workforce sooner than he thinks. □

Infrared telescope for space shuttle

THE NASA Ames Research Center has awarded a \$400,000 contract to Hughes Aircraft Co. for a design study to be carried out for an infrared telescope which could be flown in the space shuttle. The contract specifies a pointing accuracy of 1', and is expected to have an aperture in the range 1 to 1.5 m, rather larger than the 36-inch instrument which is the main tool of NASA's existing flying observatory and is mounted in a C-141.

According to a report in *Aviation Week & Space Technology* (August 19), Michel Bader, deputy director of astronautics at Ames, describes the shuttle facility as "an extension of the C-141 programme"; but the new instrument will have cooled optics and detectors, as well as appropriate changes for zero-g operation and other problems specific to the shuttle.

Grumman Aerospace Corporation will be working with Hughes on some aspects of these problems, and the study will take at least a year. Work on the hardware may not begin until well into 1977. □

Sweden's reactor problems

from Wendy Barnaby, Stockholm

THE Swedes have not yet been notably successful in the efficiency of their nuclear technology. Current frustrations in the eight-reactor building programme now under way include altering the cooling systems of two reactors, replacing a fatigued metal part in another and putting up with delays in construction in a fourth. And there was, of course, the famous Marviken reactor, whose design was so faulty that it could never be made operational and was converted to work on oil. (Critics of this waste of money labelled the project "the first oil-fuelled nuclear reactor in the world"; a designation quickly adjusted, during the oil crisis, to "the world's first wood-fuelled-oil-fuelled nuclear reactor"). But now it seems that Sweden's nuclear power programme is running into difficulties of quite another sort.

Until the last couple of years, the large-scale development of nuclear energy in Sweden was accepted by the country without controversy. The consumption of electric power was predicted to increase three-fold by 1990, but expansion of hydro-power, which provides 70% of all Sweden's electricity, was regarded as a non-starter for environmental and economic reasons. Coupled with Sweden's poverty in coal, oil and natural gas, this problem put a high priority on the development of alternative energy sources. Nuclear power was the obvious choice. The government drew up plans to build 24 reactors by 1990. The country was to approach the next century as the world's leader in reactor capacity per capita.

All this had reckoned without the activities of an increasingly vocal anti-nuclear power group, whose agitation caused parliament in May 1973 to suspend approval of the official plan until it had been presented with more comprehensive information about reactor safety and radioactive waste. The parliamentary decision did not affect the reactor in operation since 1971 or those already under construction, but postponed consideration of the future of the other sixteen until next year. The advanced state of the programme has, in effect, solved the question of whether to have nuclear power. At issue now is how much Sweden should have in the light of current safety measures.

The fact that Sweden has not yet signed a safeguards agreement with the International Atomic Energy Agency under the Nuclear Non-proliferation Treaty, and the significance that could have in a large-scale peaceful nuclear

programme (especially after the explosion of India's bomb), has not been at issue. To begin with, the Swedes are expected to initial a safeguards agreement next month; but, more importantly, all the parties to the dispute agree that Sweden will not manufacture nuclear explosives.

The dispute has caused an odd political line-up. The ruling social democrats and the conservatives both favour the large-scale development of nuclear energy, while the agrarian and communist parties are against it. The anti lobby claims widespread public support, quoting as evidence a survey commissioned by the State Power Board and private producers of energy last January, at the height of the fuel crisis, to find out whether people favoured nuclear power or not. The results were not made available to the press. Not until a 'Friends of the Earth' group forced their publication in June could it be ascertained that 59% of the sample had in fact opposed nuclear power. In spite of this support, however, the anti group is worried about the plentiful funds being made avail-

able for pro-nuclear pamphlets and educational material which will be circulated to union study-groups this autumn.

Autumn will also bring publicity for the anti group, however. A number of citizens living near a new reactor site will appeal against the decision of a so-called 'Water Court' to allow the construction of the reactors planned for the site provided that certain measures are taken to safeguard the environment. Under a law outdated since these events began, such a court was obliged to review the potential dangers threatened by any proposed building to the water environment before permission could be given for the building to be constructed. The action will take place in the court of appeals dealing with questions involving water, and the argument will of necessity be limited to those aspects of nuclear power dependent on water. The public can therefore expect to hear a lot about dangers involved in a failure of the emergency cooling system and the pollution of waterways with radioactive material, but little about other nuclear hazards.

Inflation and Imperial College

by Roger Woodham

At a time when many British universities, notably Leeds, are reporting that they are in the red by hundreds of thousands of pounds, the Imperial College of Science and Technology in London is still firmly in the black, thanks to some wise financial management a year or so ago.

In the year ended July 1973, for example, the college spent some £11.8 million but managed to salt away £635,000 to swell its reserves to £767,000. This was achieved by obliging all departments to reduce their budgets by 6%. The result was that earlier this year, with plenty of money in the bank, the college was able to embark on a modest expansion programme when many other universities were watching their margins closely.

The position now is that the reserves stand at about £250,000 and the college is faced, like other universities, with a government decision to be less than generous about supplementing the University Grant Committee's recurrent grant to allow for inflation. The government assessed the situation several months ago on the basis of the rise in costs during the calendar year 1973, with a view to paying the extra

money during the academic year 1974-75. The first estimate of the increase in costs came out at 7%—some £13.5 million—and the government declined to give the universities any more money at all. But the increase in the index was subsequently revised upwards to 10%+, representing more than £21 million. At this stage the government announced that it would provide £4 million which, together with about £3 million which the UGC had at its disposal for emergencies, just kept the total deficit to the level the government originally envisaged.

Although the Committee of Vice Chancellors and Principals welcomed the government decision to make the extra money available, its view is that the recurrent grant should be restored to its proper level and its value then maintained in real terms.

What Imperial College is now waiting to find out is how much of the £4 million will come its way. On previous experience the amount will be in the region of £150,000 to £200,000, but Mr M. J. Davies, secretary of the college, said last week that the extra money would at best keep the ship afloat and would not allow for any growth. He also described the college's remaining surplus of around £200,000 as a cushion which is rapidly disappearing. If things get much worse, he said, Imperial College will be in the same situation as other universities.

Binary weapons voted out

by Colin Norman, Washington

THE Pentagon's plan to replace its ageing stockpiles of chemical weapons with a new generation of so-called binary nerve agents received a severe blow in the House of Representatives last week, and it now seems likely that Congress will eventually kill the plan entirely. Virtually unnoticed in the welter of events being played out in Washington, the House voted to deny funds for the Army to begin producing special 155-mm artillery shells for the binary weapons.

The vote, which came on an amendment to the Defense Appropriation Bill, represents sweet victory for a group of congressmen, led by Wayne Owens of Utah, who have fought the binary programme for months on the basis that if it were allowed to go ahead it would torpedo international chemical disarmament negotiations now taking place in Geneva.

The Pentagon—or, more accurately, the Army Chemical Corps—had requested \$5.8 million this year to begin producing binary shells in the Pine Bluff Arsenal in Arkansas, with a view to replacing part of its nerve gas stockpiles with binaries in 1977. The Army began touting the advantages of the weapon late last year, by arguing that since they consist of two "relatively non toxic" components, they will be safe to store, transport and use. The idea is that the two components would be kept apart until needed on the battlefield, then they would be loaded into the binary shell and mixed together to form a lethal nerve agent.

But the House was persuaded last week that if the United States now launches a massive new chemical weapons programme, the credibility of United States negotiators in Geneva would be destroyed and the chances of reaching agreement on international chemical disarmament would be negligible. Last month Mr Nixon and Mr Brezhnev signed an agreement in Moscow to launch new initiatives to help the negotiations along, but the binary weapons programme is scarcely seen as a helpful initiative.

Another factor in last week's vote was that the Pentagon had asked for funds from Congress before the binary programme had even been approved by the Administration, a situation which several congressmen regarded as putting the cart before the horse. In fact, since Congress started considering the funding request, the Administration has been carrying out a review of the necessity for binary weapons, and the programme has already picked up strong opposition from the Arms Con-

trol and Disarmament Agency. Thus, the Pentagon's strategy seemed to be to try to get approval for the programme from Congress and then use that to bolster its case within the Administration.

Last week's House vote was, however, far from the last word on the matter, for the Senate has yet to consider the Pentagon's budget request. But it is generally believed that the anti-binary forces in the Senate will be strong enough to uphold the House's action. For one thing, an amendment will be offered in the Senate Appropriations Committee to cut off funding of binary weapons, and if that fails a number of influential Senators led by Edward M. Kennedy are prepared to take their case to a vote on the Senate floor. □

Windfall for natural resources

THE Wolfson Foundation recently announced its £1 million programme of support for research into the more efficient use of natural resources. The object of the programme is to come up with at least some answer to the problems of Britain's dependence on imported food, raw materials and energy.

This is a departure from the foundation's previous practice of giving grants for university research linked specifically to industry. The foundation received more than 150 applications for money, and in choosing the 18 projects which make up the present programme it was particularly anxious that ideas should be quickly and easily realisable commercially if the research was successful.

The projects chosen cover a wide field. Predictably, studies on various sorts of recycling and uses of wastes are much in evidence, and on the energy front there are two concerned with the use of solar energy. But money has also been found for work on the impact of motorways on agricultural land, and on cultivating the scallop, a potentially valuable export.

The Department of Agriculture at the University of Reading gets the largest slice of the cake. It has been given £250,000 for two pieces of work: one to improve the production and direct use of green leaf protein, and one for improving the production of oil and protein from seed crops. Together with a complementary study at the University College of Wales, Aberystwyth, on breeding grasses and legumes for upland areas, these lines of research could eventually lead to far more home-grown feedstuffs for Britain's animal and even human population. □

Ecological railway line

from Vera Rich

THE new branch of the Trans-Siberian Railway, which is to run via Ust-Kut on the Lena, skirting the north of Lake Baikal, and across some 1,500 km of the Siberian taiga to join the existing tracks at Komsomolsk on the Amur, is clearly being treated as a prestige project by the Soviet media, which faithfully report every step in its progress.

This publicity is, perhaps, not surprising, since the projected line will run through some of the most promising of the undeveloped areas of Siberia. The line will, however, pass through a region which is a constant focus of attention for ecologists.

Lake Baikal has, of course, been subject to railway 'pollution' since the trans-Siberian route was envisaged in 1891. Indeed, in the early days, the track actually ran across the lake—rails were laid on the ice in winter and ferry boats were used during the summer (with a twice-yearly break in service during the thaw and freeze-up).

Conservation has now become an emotive concept, and the planners of the new line have not only taken it into account in their proposals for the line, but have also taken considerable care to be seen to be taking it into account.

Mikhail Reks, the chief engineer of the Baikal project, has assured world opinion (through the Novosti agency) of the environmental protection measures to be taken. No tree felling is to be permitted on slopes with gradients exceeding 15°, or in valley bottoms, to obviate erosion caused by avalanches and mud streams. Special dams and trenches in permafrost areas will protect the soil—as well as ensuring the safety of the railway itself. The banks of the reservoir on the River Zeya are to be reinforced, and it is stated that the massive bridge-building programme involved (over 140 bridges in all) will tend to stabilise the channels of the Siberian river beds, and thus reduce erosion.

The wild life of Siberia is to be left as undisturbed as possible—although Reks admitted that the line will to a certain extent "press back" many species. One wonders however, how the construction workers themselves will react to the ruling on insect life. For, in order to disturb the ecological balance as little as possible, no insecticides may be used, not even against the traditional curse of Siberian life—mosquitoes. The only means of self defence permitted, according to the official ruling, will be mosquito nets and special repellent creams. □

correspondence

Chile: for . . .

SIR,—I have recently read your editorial of May 3, on academic freedom in Chile, and would like to make some comments on it.

This is the third occasion I have come to Chile to lecture, the previous visits being in 1970 (before Allende's election) and 1971 (under the UP government). I also lectured here in 1965 (shortly after Frei's election) but not with a contract. I cannot claim to know the state of all the branches (*sedes*) and faculties of the University of Chile or other universities, but I am tolerably well acquainted with what goes on here. I can assure you that as far as this department is concerned, your article is almost totally untrue.

I have seen no military in or near the Faculty in my two months here, although I do understand that they searched it for arms a couple of days after the coup, since when they have not returned. Not one member of staff of this department has been dismissed for political or any other reasons.

Actions 'such as not taking part in the anti-Allende demonstrations' are not 'now retrospectively considered illegal'. Hardly anyone in the department ever took part in such actions. On the contrary a considerable number of the staff and perhaps 50% of the students regularly took part in pro-Allende meetings or demonstrations. To all those UP sympathisers or militants (not to mention the apolitical) who stay unchanged in their academic posts, your suggestion that they 'remain at the universities in puppet roles' is insulting. You conclude the phrase by adding 'organising research according to the junta's decree, teaching what the junta thinks fit to be taught'. The courses here are submitted to no one, military or otherwise, for approval. My own course has not been reviewed even by the director of the department.

Your report must certainly be true for some academic institutions (because I cannot believe the entire international press is misinformed) but it is nowhere near the whole truth. Either you too easily believe the statements made in Europe by refugees, genuine or otherwise, without attempting to verify them, or you are not concerned with straight reporting and are motivated by political considerations. If the latter is true and *Nature* has ceased to be a scientific journal to become a political one, may I, as an Irishman,

suggest you focus your concern about military misbehaviour on your own army for which you are indirectly, and many British scientists directly responsible, rather than on the army of a country on the other side of the globe where you apparently have never set foot.

I am no apologist for the military junta; on the contrary I am a strong supporter of the ideals of social justice which Allende claimed to support. However honesty forces me to admit that the most charitable interpretation of the cause of his regime's collapse was its catastrophic incompetence. The chaos that reigned in 1973 would have provoked a coup in any other Latin American country, and most European ones too. That said, and recognising the impertinence of making comments on the internal affairs of a foreign country, I unreservedly condemn the brutalities, vengeful actions and plain stupidities attributed to the authorities at various levels since September 11. Perhaps, following the above, I can best demonstrate my conviction that academic freedom and 'intellectual life' in Chile is *not* 'dead' by signing myself openly

Yours faithfully,

W. F. L. PURSER

*Universidad de Chile,
Santiago de Chile*

. . . and against

SIR,—The Chilean replies to the letters published in *Nature*, criticising the regime, although insulting the intelligence of your readers, underline the spirit of a totalitarian regime, a trivial phenomenon these days. However, there is no necessity to refute arguments which only underline how ideological fanaticism can deform judgement.

It seems more important to stress the need for the scientific community, which is rightly reluctant to become involved in political controversy, to assert that it cannot remain indifferent when individual freedom is at stake under any politico-economical order, religious or social prejudice. It is a matter of dignity for scientists to know that the torturers' representatives be at least excluded from their community, if more drastic action cannot be taken.

As for those, whether nationals or 'multinationals', who support regimes of the Chilean or Czechoslovakian type, they would be well advised to have the decency to spare us the nausea of their

public apologetic justifications. They might also be advised to consider that Portugal and Greece are perhaps not just mere accidents.

Yours faithfully,

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Publish or perish

SIR,—How can we escape from the tyranny of the Science Citation Index (how many citations did your papers get last year?) and the general publish-or-perish rat-race?

I suggest a procedure by which a stable and well-established department might contract out. Let all papers from the department be published under the same fictitious name, as is done by the pioneer French school of mathematicians who are Nicholas Bourbaki — a general who, when defeated, tried to shoot himself but missed. What effects might follow?

We might build one substantial scientist out of several mediocre ones, whose success might encourage the others. As Blackett has pointed out: "a first-class laboratory is one in which mediocre people can do outstanding work".

The Matthew Principle (Matthew, 25: 29) of R. K. Merton, "to every one that hath shall be given . . ." will be turned to general advantage since $(A + B + C + \dots)^x > A^x + B^x + C^x \dots$ (if $x > 1$).

The general standard of papers might be increased and their numbers reduced by taking off some of the pressure on the individual to rush into print.

Multiple subscriptions to journals and societies could be reduced.

The promotion scheme based on published papers would be confounded, perhaps forcing the consideration of persons as persons.

There has been much talk of the commonwealth of science, but who will be the second to set up a scientific commune? I am sure that common scientific property will be as strongly opposed by the establishment as the commonality of the property of Christians was opposed by the Church of England (Article 38).

Yours faithfully,

ALAN MACKAY

*Department of Crystallography,
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news and views

Transfer RNA revisited

It is now some six years since the first successful crystallisation of transfer RNA was reported by a group of workers at the MRC Laboratory of Molecular Biology, Cambridge (*Nature*, **219**, 1222; 1968). Subsequently a large number of both mixed and purified tRNA crystals have also been obtained. There has, however, been a central problem in obtaining crystals of sufficient quality. Only this would enable an X-ray structural analysis to provide a detailed picture of the molecular architecture of tRNA. In 1971, Kim, Rich and their associates, at the Massachusetts Institute of Technology, reported that they had obtained highly diffracting crystals of the tRNA from yeast which codes for phenylalanine (*Proc. natn. Acad. Sci. U.S.A.*, **68**, 841; 1971). These workers then proceeded to analyse these crystals, and reported obtaining electron density maps at successively 5.5 Å and 4.0 Å resolution, culminating in a 3.0 Å map using the standard isomorphous replacement methods of protein crystallography (*Nature*, **248**, 20; 1974). Each improvement in resolution enabled the form of the molecule to be visualised more clearly, and their final electron density map showed the molecule to have an L shape, with two stems of double helical oligonucleotides in each arm. The polynucleotide chain was clearly seen, except in the nonhelical loop regions of the molecule.

The tRNA species that the MIT group has been investigating crystallises in many (up to twelve) distinct crystal forms. This intense polymorphism raises the question whether it is a reflection of merely alternative packing modes within the crystal lattice, or a consequence of conformational changes within the tRNA molecule. Cramer *et al.*, in a thorough examination of crystallising conditions for eight of these polymorphs, have remained undecided on this question (*Biochim. biophys. Acta*, **349**, 351; 1974). The MIT group has attempted an answer by extending its original analysis, on an orthorhombic form, to the monoclinic form. Both of these polymorphs diffract X rays well, to a resolution of better than 3 Å. So it is reasonable to suppose that the molecules in both forms are packed reasonably well. Furthermore, the two forms are related in terms of unit cell dimensions, suggesting closely related structures. Kim *et al.* used simple molecular replacement procedures in order to see how their orthorhombic molecule fitted the data from the monoclinic crystals. They obtained reasonably good fits and concluded that the structure was essentially unchanged on going from one form to another. The only proviso was that there were possibly some small undefined changes in the region of the anticodon loop.

The Cambridge (England) group has now reported their independent 3 Å analysis of the monoclinic form (Robertus *et al.*, *Nature*, **250**, 546; 1974). Again, the method of isomorphous replacement has been used to solve the structure. The outline shape of the molecule was obtained by tracing the ribose phosphate backbone, particularly in the four stem regions where it was most discernible. Clearly, compared with a polypeptide backbone in a protein, polynucleotide chains are considerably more difficult to follow. This is mainly because of the close similarity of ribose, phosphate, purine and pyrimidine groupings when seen at a resolution of 3 Å. It did not prove possible to trace unambiguously and

completely the chain in the non double-helical D and T ψ C loops; the MIT group has similar difficulties in these regions of the molecule. The monoclinic form is very similar in overall shape to the Cambridge (Massachusetts) orthorhombic findings. The fact that the former shape has been called a T, and the latter an L, is to some extent a matter of semantics. There are, however, a large number of significant differences between the two structures. Perhaps the most important concerns the orientation of one of the double-helical stems, the so-called D stem, which differs in the two by 90° in one direction. It is noteworthy that the main helix directions now all agree well with Levitt's helix search locations (*J. molec. Biol.*, **80**, 225; 1973). The relative placing of the other three stems is not disputed. There is a disagreement about the fitting of the nucleotide sequence to the chain, by one (and sometimes two) residues, virtually throughout the entire molecule. Robertus *et al.* consider that these shifts in the chain assignments have necessitated revision of many of the earlier structure conclusions. For example, whereas the helical stems were previously considered to be irregular, they are now found to conform to the standard classes: the amino acid and the T ψ C stems together form a twelve base-pair-long double helix of the 'A' form. The functionally important anticodon loop seems to have more order than previously described with stacking on the 3' side of its stem. This, together with the quasihelical geometry of the anticodon bases, is one of the many satisfying features of the new model. The Cambridge (England) group detail the features of the molecule which help to maintain its structure. These are additional base pairings, and also base triplets—many of a novel nature—as well as numerous stacking and intercalative interactions.

These tertiary interactions cumulatively have the effect of folding and maintaining the familiar tRNA cloverleaf into a molecule with essentially three major interlinked substructures. These are, firstly, the long, almost perfect double helix formed by stacking the acceptor and T ψ C stems. The D stem is augmented by several unusual base pairs and postulated triplets, some involving their own loops, and some the variable loop, and is attached to the long helical segment almost at the middle. This forms the T junction. The anticodon stem then extends outwards from the augmented D helix, with the helices separate and non-collinear. Indeed, the anticodon helix (with its loop at the far end of the molecule) seems almost to be hinged on to the D stem, with a consequent implication of mobility, possibly during protein synthesis.

This new model has also been examined for consistency with the extensive chemical modification data which now exist for tRNAs (Robertus *et al.*, *Nucleic Acids Res.*, **1**, 927; 1974). It has now been assumed that bases susceptible to modification are those not involved in tertiary interactions. On this basis, double-helical residues would be unaffected, as indeed they are. Similarly, those bases involved in the tertiary interactions detailed in the X-ray model would not be modified, as indeed they are not. The reactive bases are the ones that are not only uninvolved in tertiary interactions but are on the surface of the molecule. The model is also of interest in that it suggests that many of its structural features are common to all tRNAs. The bases which are either invariants in all tRNAs, or are conserved as purines or pyrimidines, are mostly involved in the tertiary interactions. Thus, the pattern of

molecular folding, so dependent on these, may well be at least similar for the majority of tRNAs.

The Kim and Rich group have very recently made an additional contribution to the subject of tRNA structure (*Science*, **185**, 435; 1974). In what may be seen as a counter to the criticisms of their structural model, they have presented a comprehensive analysis of its tertiary structure. This necessitated revision of a number of the residue assignments, although the overall chain tracing remains generally unaltered. The tertiary base-pairing and stacking interactions now found are mostly identical to those in the Cambridge (England) model, although a number of differences in interpretation still remain. In general the two models are now very similar. Consequently, it is now possible to state, with some considerable measure of confidence, that the basic structure of a transfer RNA has been established.

STEPHEN NEIDLE

Molecular neuroanatomy

NEUROANATOMY has relied for many years on a limited number of classical staining methods, the chemical bases of which have remained largely obscure. During the past few years, however, the field has seen a quiet revolution as several powerful new techniques have developed as a result of a greatly increased understanding of the special biochemical properties of nerve cells. Many of these new methods make use of the fact that neurones of different types are biochemically differentiated in the sense that each type manufactures and stores only one of a series of potential transmitter substances. Great progress has stemmed, for example, from the development of a histochemical fluorescence technique for visualising catecholamine and indolamine-containing neurones and their fibres (Falck, *Acta physiol. scand. (second suppl.)*, **197**; 1962).

Such specific staining methods have so far not been available for neurones using other transmitters. One approach of general applicability is the development of immunofluorescent histochemical techniques, using antibodies directed against some protein that is characteristically localised in a given transmitter-specific type of neurone. Thus, antibodies to the enzyme dopamine- β -hydroxylase have been used to identify noradrenaline-containing neurones in tissue sections (Fuxe *et al.*, *Progr. Brain Res.*, **34**, 127–128; 1971). Progress in the application of such methods to other transmitter types has been reported recently. Saito *et al.* (*Proc. natn. Acad. Sci. U.S.A.*, **71**, 269–273; 1974) describe the use of antibodies to the enzyme glutamic decarboxylase for the immunofluorescent identification of neurones that use gamma-aminobutyrate (GABA) as their transmitter and Eng *et al.* (*Nature*, **250**, 245–247; 1974), McGeer *et al.* (*J. Pharmic.*, **5**, Suppl. 1, 54; 1974) and Rosser *et al.* (*FEBS Lett.*, **36**, 43–48; 1973) have prepared antibodies to purified choline acetyltransferase and described their use for the identification and mapping of cholinergic neurones in the central nervous system (CNS). These neurones have hitherto been identifiable only by histochemical methods for the enzyme acetylcholinesterase; the localisation of the biosynthetic enzyme choline acetyltransferase, however, promises to be a more specific and reliable biochemical marker for such structures, since this enzyme occurs exclusively in cholinergic neurones in the CNS.

These new methods for identifying transmitter-specific neuronal pathways have been and will continue to be of immense value for mapping the distribution of such pathways in the CNS. At the same time two other approaches,

which represent more general means of determining the axonal projection of groups of neurones in the CNS, have been developed. Both approaches make use of the specialised transport systems that exist for the movement of substances along nerve axons. Protein synthesis in neurones is confined largely to the cell body region of the cell, and there is continuous export of newly synthesised material from the cell body along the axon processes to the nerve terminals. This orthograde flow of material can be used to trace the axonal projections of neurones by pulse-labelling the cell bodies with a radioactively-labelled amino acid and then following the transport of labelled protein into such projections. This usually involves a local microinjection of isotope in the region of a particular brain nucleus, followed by autoradiographic examination of the distribution of label in various potential areas remote from the site of injection (Cowan *et al.*, *Brain Res.*, **37**, 21–51; 1972). Another more recently recognised transport mechanism operates by as yet unknown means to transport certain proteins from the nerve terminals in the retrograde direction towards the cell body regions of neurones. By using an easily identified marker protein not normally present in the CNS, such as horseradish peroxidase, it is thus possible to determine the cells of origin of fibre tracts in CNS. This substance is applied by local injection into a projection area, and then peroxidase-containing cell bodies are identified in remote brain areas. (La Vail *et al.*, *Brain Res.*, **58**, 470–477; 1973).

Apart from methods that allow the mapping of populations of neurones organised in specific pathways, important developments in techniques that reveal the detailed anatomical features of individual neurones have also been made. Stretton and Kravitz (*Science*, **162**, 132–134; 1968) found that microinjection of the fluorescent dye procion yellow into single neurones of the lobster nervous system allowed the subsequent visualisation of even the finest branches of the axonal and dendritic tree emanating from such neurones. Procion yellow diffuses readily into such processes, and the neurone remains electrically excitable during the process. This technique has been widely applied to invertebrate and vertebrate neurones, with results of often breathtaking clarity (*Intercellular Staining Techniques in Neurobiology*, edit. by Kater and Nicholson, Springer-Verlag, Berlin, 1973).

Autoradiography has also been used to trace the dendritic ramifications of spinal cord motoneurones following intracellular injection of radioactively labelled amino acids (Globus *et al.*, *Brain Res.*, **11**, 440–445; 1968). In last week's edition of *Nature* (**250**, 655–658; 1974) Pentreath and Cottrell described a further modification of this approach which depends on the injection of radioactively-labelled transmitter or transmitter precursor into single cells. This has the advantage that the transport of transmitter molecules along axons occurs more rapidly than that of labelled proteins and a higher proportion of the injected material may be transported over quite long distances in this manner. Pentreath and Cottrell worked with a large neurone in the cerebral ganglion of the snail *Helix pomatia*. There is one such giant neurone on each side of the ganglion, and the cells are known from previous neurophysiological and biochemical studies by the authors to use 5-hydroxytryptamine as their transmitter. After the microinjection of tritiated 5-HT or the precursor 5-hydroxytryptophan, using electrophoretic expulsion from the tip of a fine glass electrode inserted into the cell body, the labelled amine was rapidly transported away from the cell body into the axonal system. Within 10–15 h after injection label had penetrated into the fine terminals of the neurones, some of which were several centimetres from the site of injection. Using autoradiographic analysis of serial tissue sections the entire axonal projection could be mapped. The projection from each giant neurone was found to be complex, consisting of several large axonal processes and numerous smaller

branches. Some axons projected to the buccal ganglion, in which 'follower' cells have previously been identified in neurophysiological studies, others crossed the midline, and several terminated in various muscles concerned with feeding behaviour in the mollusc.

In addition to light microscope autoradiography, Pentreath and Cottrell were also able to use electron microscopic autoradiography to investigate the fine structure of some of the labelled terminals. All of the injected label appeared to be confined to the injected neurones, and this method thus offers a relatively rapid and highly specific means of

determining the various presynaptic terminals emanating from an identified single neurone.

It is clear that neuroanatomy has felt some of the impact of the molecular biology era, and that the battery of new techniques that have recently become available will stimulate an upsurge of activity in this area. Such a revival will come none too soon if one is to begin to understand the functional significance of the various chemically specific pathways of neurones that are now known to exist in the CNS.

L. L. IVERSEN

Clock and calendar in SI units

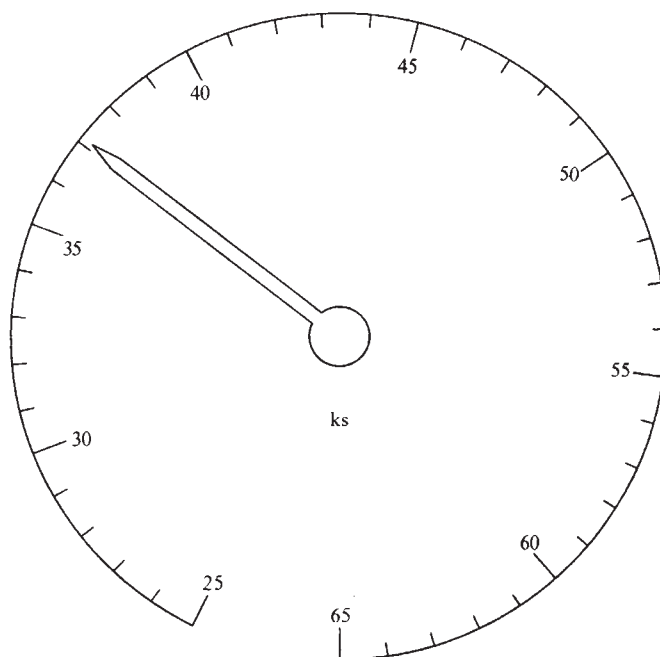
In the SI system, one gives the time of day and date in kiloseconds, megaseconds and gigaseconds. The appropriate daytime clock has no minute hand and has a new face graduated 25–65 ks (see figure); if the range 0–86.4 ks was completed, the clock would also be suitable for night use. One's schedule might be: 25 ks, breakfast; 30 ks, start work; 45 ks, lunch; 60 ks, stop work; 65 ks, supper; 80 ks, retire.

On the calendar (see Table), one dates by the megasecond, stating a number under 100 with one decimal place. This increases daily except Sunday by 0.1 Ms. Thus, the eight days July 3–10, 1974, are 77.6, 77.7, 77.8, 77.9, 77.9+, 78.0, 78.1, 78.2 Ms. A + distinguishes Sunday. 0.1 Ms, however, must also be added on six Sundays out of 125 (since 1 week = 0.6 Ms = 4.8 ks). The megasecond date then never differs from the actual time each day begins by more than 90.4 ks. After making a correction for this difference, one adds the time of day (see figure) to fix any instant absolutely.

This continuous calendar does not begin anew each year. Subtracting the megasecond at the new year from the current megasecond gives the time of year, useful in astronomy, weather, biology and farming. To place a date in history, one states the gigasecond to the nearest 0.1; for 1972–74 this is 62.2 Gs.

The many advantages include elimination of timers graduated in diverse units, and of unsystematic derivatives such as revolution per minute and kilowatt hour. Moreover, 62 278.2756 Ms has fewer symbols and easier arithmetic than 11:40 a.m. July 10, 1974. Neither change in work schedules nor internationally agreed reform are needed; scientists and engineers can begin to use a SI clock and calendar today.

CHARLES E. CHAFFEY



Partial SI calendar

	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Date 1974
Ms	77.3+	77.4	77.5	77.6	77.7	77.8	77.9	July 6
ks	69.6	56.0	42.4	28.8	15.2	1.6	-12.0	
Ms	77.9+	78.0	78.1	78.2	78.3	78.4	78.5	July 13
ks	74.4	60.8	47.2	33.6	20.0	6.4	-7.2	
Ms	78.5+	78.6	78.7	78.8	78.9	79.0	79.1	July 20
ks	79.2	65.6	52.0	38.4	24.8	11.2	-2.4	
Ms	79.1+	79.2	79.3	79.4	79.5	79.6	79.7	July 27
ks	84.0	70.4	56.8	43.2	29.6	16.0	2.4	
Ms	79.7+	79.8	79.9	80.0	80.1	80.2	80.3	August 3
ks	88.8	75.2	61.6	48.0	34.4	20.8	7.2	
Ms	80.4+	80.5	80.6	80.7	80.8	80.9	81.0	August 10
ks	-6.4	-20.0	-33.6	-47.2	-60.8	-74.4	-88.0	

Add 62.2 Gs. New Year was 61.8 Ms. The beginning of each day is the sum of the large figure (in Ms) and the small figure (in ks).

Primitive but not simple

THE study of human embryonic haemoglobin, initiated principally by Huehns and his collaborators, starts from the demonstration that biosynthesis of a 'primitive' or ϵ polypeptide chain precedes that of the γ chains of human foetal haemoglobin (Hb-F, $\alpha_2\gamma_2$). At birth Hb-F normally comprises some 80% of the total haemoglobin, the remainder being adult haemoglobin (Hb-A, $\alpha_2\beta_2$), as the biosynthesis of β chains is switched on, and that of γ chains starts to decline at 6 months' gestation. The ϵ chain occurs as Hb-Gower 1 (ϵ_4) and Hb-Gower 2 ($\alpha_2\epsilon_2$) and its formation has completely stopped at a gestational age of less than 3 months. There is also evidence that synthesis of the α chain is preceded very early in gestation by another type of chain, originally denoted as x but now designated ξ . This chain is found in the haemoglobin species Hb-Portland 1 with composition $\xi_2\gamma_2$, believed to be present in early human embryos, and also found in stillborn infants

with erythroblastosis foetalis caused by homozygous α -thalassaemia 1, where α -chain synthesis is completely inhibited.

The practical problems associated with the study of human embryonic haemoglobins can be circumvented in animal studies, and Melderis, Steinhilber and Ostertag, of the Max-Planck Institute for Experimental Medicine, Göttingen, now report (see page 774 of this issue) evidence for a unique x -type globin chain in early mammalian embryos (BALB/c mice and New Zealand white rabbits). The x chains of these two species have closely related sequences, similar to that of the human ξ chain of Hb-Portland 1. Detailed analysis of the complex systems—three embryonic species in the mouse and six in the rabbit—leads to the conclusion that there are at least two different ϵ chains, and that x - and α -chain synthesis in both species is inversely correlated, hence the first chain takes the place of the second during early embryo-

genesis. The x chain is now to be regarded as a α -type chain, and there is more sequence similarity between x chains of different species, than between the x and α chains of the same species. This indicates an early evolutionary divergence of x - and α -chain genes and constitutes a further example of globin gene duplication during evolution; compare the findings of Schroeder, Huisman and colleagues on the duplicated $^0\gamma$ and $^A\gamma$ genes for the γ -chain of human Hb-F.

The Göttingen work confirms the indication from the earlier work on human embryonic haemoglobins that there is an α -type x (or ξ) chain synthesised in the nucleated erythroid cells derived from the yolk sac during early stages of mammalian embryogenesis, and preceding the synthesis of α -chains proper. The presence of an ϵ_4 species in human but not in mice or rabbit embryos remains to be explained.

From a Correspondent

Topology of crystal grains

from Robert W. Cahn

It is one of the paradoxes of the history of science that the rigorous quantitative treatment of the behaviour of large populations of molecules preceded by many years the similarly rigorous description of the individual molecules themselves; yet the kinetic theory of gases implies the extraction of orderly and predictable behaviour from myriads of random motions and collisions, whereas molecules are all identical. The resolution of the paradox lies in the fact that in the kinetic theory, molecules are treated virtually as independent, featureless particles, and therein lies the tractability of the whole approach. A million particles spell simplicity; one molecule spells complexity.

With crystals, the sequence is reversed. A large number of crystal structures had been accurately determined before the collective behaviour of populations of crystals began to be understood. The metallurgist recognises two distinct forms of such collective behaviour: first, there is 'Ostwald ripening', a poetically metaphorical term for the Matthew principle applied to a population of spherical crystallites of varying radii dispersed in a matrix; the larger ones grow at the expense of the smaller, essentially because of a radius-

dependence of the solubility of the particles in the matrix. (Water droplets in a cloud behave in an essentially similar way.) The rigorous treatment of this very important metallurgical process is now well understood.

The second form of collective behaviour is grain growth. A piece of a pure metal consists of a population of crystal grains all sharing the same crystal structure but of different sizes, shapes and orientations. The grains grow from independent nuclei and as they impinge, grain boundaries are formed. The interfaces may be plane or curved, and bear no relation to the regular lattice arrangement of atoms: "There's no art to read the grain's construction in the face". Here, also, the Matthew principle operates: if a piece of metal is heated, the larger grains grow at the expense of the smaller through the migration of grain boundaries, and the average grain size progressively increases.

Grain growth has been studied micrographically for many years, both for its intrinsic interest and because of its practical influence on metal working, on the behaviour of nuclear fuel elements, in powder metallurgy and elsewhere. It has long been recognised that the mean grain diameter varies with time according to $\Delta D = kt^n$, where n falls in the range $1/3$ – $1/2$. The problem is to understand why. It is a conceptually more difficult problem than the kinetic theory of gases, because

crystal grains are not independent and separate particles, but connected polyhedra. When one grain changes shape and size, the neighbours of necessity change too. An assembly of grains is like a nuclear reactor: a change in neutron absorption in one small corner soon leads to a change in neutron flux throughout the reactor. Similarly, an instability at one corner of one grain quickly spreads through the population.

The key to an understanding of the problem is its topology. A population of polyhedral grains can be characterised by the number of grains, faces and vertices, and by the relations between these quantities. In particular, interest attaches to the mean number of faces per grain and the distribution of this number among the grain population. Topological principles were first applied, to assess the stability of a grain population, by C. S. Smith in 1952. He recognised that grain growth stems from disequilibrium at edges where three grains meet and at four-grain corners. Unless three boundaries meeting at an edge are mutually inclined at 120° the edge must move and the boundaries become curved. The curvature itself introduces instability; indeed, curvature and non-equilibrium edge and corner configurations are the fuels of grain growth. The nearest approach to equilibrium obtains in a population of fourteen-sided polyhedra of a particular shape.

In a brilliant paper Rhines, Craig and

Dehoff (*Metall. Trans.*, **5**, 413; 1974) apply topological analysis to grain growth in a highly illuminating way. Their article is based upon an experimental study of successive stages of grain growth in aluminium, using the technique of serial sectioning; the technique depends on a thorough mastery of the theory of quantitative metallography which allows two-dimensional measurements in the microscope to be converted into reliable three-dimensional geometrical statistics. In their laboratory at the University of Florida, the authors have honed this technique to a fine cutting edge. They are able to determine the total grain boundary area, mean boundary curvature, distribution of the number of faces per grain, as well as the true mean volume per grain, as a function of time.

By combining experiment with topological analysis, Rhines *et al.* are able to introduce the concept of a "structural gradient" which is essentially a measure of the mean deviation from equilibrium of the entire grain structure. It is equal to the product of the total mean curvature and the surface area per grain. This structural gradient determines the rate of steady-state grain growth, and remains unchanged because the form of the distribution of different grain shapes remains unaltered as grain growth proceeds. All this is made topologically clear by the authors. They also show in a simple and elegant fashion that the number of grains eliminated when a grain boundary sweeps through unit volume of material is a constant, independent of the mean grain size. This very important theoretical result will have a number of important applications in materials science (for instance, in connection with sintering of powders, in which grain growth plays a crucial part).

By putting the various parts of the analysis together, the authors find both theoretically and experimentally that grain growths follow the law $\Delta D = kt^{1/3}$, when the 'diameter' D is expressed as the cube root of the mean true grain volume. The apparent grain diameter derived from intercept analysis on a single two-dimensional section gives an index rather higher than $1/3$, which indicates that good quantitative metallography requires more expertise than most investigators possess. The authors point out that "it has not been required, in developing the foregoing rate law, to introduce any arbitrarily adjustable parameter, as has been done in the usual expression of grain growth kinetics". Theirs is an impressive achievement.

A recent attempt to apply purely statistical principles to grain growth (Louat, *Acta Metall.*, **22**, 721; 1974) is an instance of the type of analysis at which the Florida authors, by implica-

tion, cock a sceptical eyebrow. This is not to say that the statistical approach has no value: for instance, Weaire (*Metallography*, **7**, 157; 1974) shows how statistical arguments can be combined with topological ones to assess whether a distribution of grain shapes deviates locally from randomness.

Another recent article of striking originality on a related theme is by Morrall and Ashby (*Acta Metall.*, **22**, 567; 1974) who consider an assembly of fourteen-sided polyhedra in near equilibrium, as per Smith's specification, and then introduce a number of thirteen or fifteen-sided grains, or other more serious 'grain defects'. The grain structure is then denoted by joining the centres of all neighbouring grains, through their common boundaries, by a network of lines. These lines form a lattice ('lattice graph') with dislocations wherever there is a grain defect. These dislocations can move conservatively (using the term in the special sense of dislocation theory); this corresponds to grain displacement of the type found in superplasticity, without change in the number of grains. Dislocations can also move by climb, which implies the disappearance of some grains in 'real space' and therefore corresponds to grain growth. The authors build on an earlier analysis by Hillert of grain growth in two dimensions, where a set of perfect hexagons is disturbed by some rogue pentagons, and the like. For three dimensions, they relate, as did Hillert for two dimensions, the rate of grain growth to defect density, that is, to the density of dislocations in the lattice graph. They predict that if the defect density is constant, $\Delta D = kt^{1/2}$, while the index $< 1/2$ if the defect density decreases during grain growth.

Morrall and Ashby's analysis represents an interesting link between the purely topological and purely statistical approaches. Since the Florida authors showed experimentally that the grain shape distribution is invariant with time (that is, the grain defect population is invariant too) Morrall and Ashby's analysis predicts $\Delta D = kt^{1/2}$, which is inconsistent with the experimental findings of the Florida group. The problem of grain growth has plenty of mileage left for those investigators who can master the requisite degree of subtlety.

Spartina's success in salt marshes . . .

from Peter D. Moore

THE grass genus *Spartina* is a remarkable one, both in terms of its world-wide success as an intertidal, salt-marsh species, and because of its very high production rates in such situations.

In the British Isles the spread of *Spartina anglica* ($= S. townsendii$), particularly during the early part of this century, is well known. The success of this species may be attributed to its remarkable capacity for strong growth over a wide range of levels in the salt marsh as well as to its salinity tolerance. Once established it forms dense clumps, which Ranwell has estimated may expand at a rate of 2% per annum on an area basis (*J. Ecol.*, **52**, 95; 1964). It is thus a powerful competitor, often forming dense, single species stands over wide areas.

On the east coast of North America there are several species of *Spartina* which show a tendency towards localisation within specific zones of the salt marsh. For one of these species, *S. alterniflora*, there are now a number of estimates for annual shoot production. Production rates, as indicated by above ground standing crop at the end of the growing season, are greatest in the southern States: for example, Teal (*Ecology*, **43**, 614; 1962) found standing crops of 1,290 g m⁻² dry weight in Georgia, whereas in Rhode Island Nixon and Oviatt (*Ecol. Monogr.*, **43**, 463; 1973) found 840 g m⁻². These figures are fairly representative of the falling production of the species as one moves north (see the literature review by Keefe, *Mar. Sci.* **16**, 163; 1972).

More detailed studies of the seasonal changes in productivity and the chemical composition of *S. alterniflora* in a New Jersey salt marsh have been carried out by Squiers and Good (*Chesapeake Sci.*, **15**, 63; 1974). Production in early spring was 8 g m⁻² d⁻¹ rising to 26 g m⁻² d⁻¹ in early summer. The peak standing crop was 1,592 g m⁻², but in late summer this trend was reversed and there was a net loss of dry matter at a rate of 13 g m⁻² d⁻¹. This loss could be caused by enhanced respiration rates relative to photosynthesis or, more likely, the death and loss of lower leaves. Since *Spartina* is not heavily predated by herbivores, the fall of litter represents the most important channel whereby the energy fixed in photosynthesis is passed on to heterotrophic organisms.

There is also a build up of protein, reaching maximum levels in the early spring. Presumably the plant has a strong demand for soil nitrogen at this period since this nutrient could become limiting to growth later in the season. Indeed, Sullivan and Daiber (*ibid.*, **15**, 121; 1974) have found that production rates in the dwarf form of *S. alterniflora* are limited by nitrogen supply in the growing season.

These data confirm the assertions of Odum that the salt marshes of the eastern United States are among the most productive habitats in the world. They also point to *Spartina* as a key

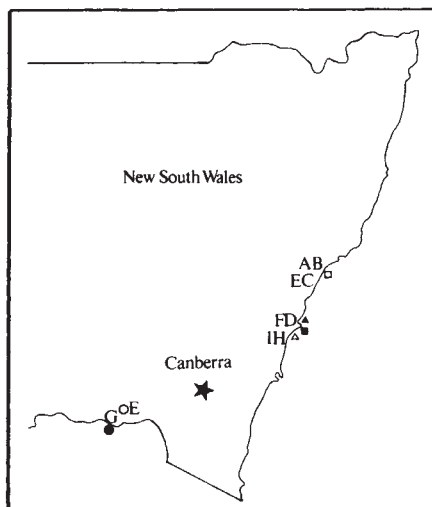
species in this high productivity. Recent studies on the physiology of *S. anglica* in Britain have suggested that this is one of the few temperate grasses which has adopted the C_4 system of carbon assimilation (see *Nature new Biol.*, **246**, 98; 1973), a mechanism frequently associated with high productivity. It is likely that this propensity for CO_2 fixation by the C_4 pathway is shared by other members of the grass *Spartina* which could account, in part, for its success in temperate salt marshes.

... and alligator weed spreads in Australia

from John Hockley

ALLIGATOR weed (*Alternanthera philoxeroides*), a normally harmless aquatic weed, is spreading rapidly in the rivers and canals of eastern Australia; it is blocking irrigation channels and is threatening the fishing, prawning and oyster industries along the Georges River near Sydney in New South Wales. The natural home of this species of weed, which belongs to the family Amaranthaceae (Duke, *Ann. Mo. bot. Gdn.*, **48**, 43; 1961), is South America and it was first noticed in Australia in the mid-1940s when it was seen growing on heaps of ballast dumped ashore at Carrington near Newcastle (see map). It seems to be spreading rapidly because although its seeds are infertile in Australia, it can reproduce vegetatively, its natural insect enemies are absent and it is able to flourish in a variety of habitats—it does particularly well in rivers enriched with sewage effluent.

The weed has been reported from places as far apart as Grafton, on the north coast of New South Wales; Williamstown, north of Newcastle, where it is blocking drainage canals; and Albury on the Victorian border, where it is not only a menace along irrigation canals, but also a possible threat to the Murray and Murrumbidgee Irrigation Areas. The largest



Recorded occurrences of alligator weed in New South Wales. 1946(A), 1962(B), 1965(C), 1969(D), 1970(E), 1971(F), 1972(G), 1973(H), 1974(I). □, Newcastle District (Williamstown, Carrington and Maitland); ▲, Carnarvon Golf Club (Lidcombe); ■, Duck Creek (Clyde); △, Georges River (Casula, Glenfield and Liverpool); ○, Holbrook; ●, Lake at Woomargama (Albury).

infestation is along the Georges River on Sydney's south-western boundary, where the optimum environment, one containing a high level of nitrogen, is provided by the effluent from the many sewage treatment works that empty into the river. In addition to the threat to the fishing industries, recreational activities such as swimming, water skiing and rowing along the river are being affected. Along the Georges River, alligator weed will grow on land as well as in freshwater and is tolerant to salt water (up to 10% salt by volume).

Various control measures have been tried with mixed success. Mechanical control is costly and usually has only a short term effect. Chemical control is only partially successful because only that part of the plant above the water can be killed. The stem that floats just below the surface of the water remains to shoot again. Trees, such as eucalypts

and she-oaks, and other plant life on the banks are very susceptible to the herbicide used to control alligator weed. Another undesirable aspect of this 'knock-down' type chemical control is the unpleasant smell produced by the rotting leaves that sink to the bottom of the river. The decaying leaves take oxygen out of the water, rendering it unsuitable for fish life.

Introduction from South America of two small insects that are the natural enemies of alligator weed may assist in controlling the infestation. The adults and larvae of the flea beetle (*Agasicles* spp.) are specific to alligator weed and feed on its leaves. The phycitid beetle (*Vogtia malloi*) bores into and eats the hollow stem of the weed allowing water to enter. After a period of time the remains of the stem become waterlogged and the plant drowns, as the leaves sink below the surface of the water. It seems likely that alligator weed will be controlled by biological means when its natural insect enemies are introduced to Australia in the near future.

Hedging one's evolutionary bets

from Montgomery Slatkin

ALTHOUGH population geneticists are not yet sure how natural selection acts on most of the genome—or even if it affects that much of the genome—there have been many predictions of the consequences of different kinds of selection. The hope has been that such models would help one to understand the dynamics of the gene pool of a population and would identify the kinds of natural selection which have been most important in evolution. Such models, however, despite fifty years of development are still far from that goal because of the inherent complexity of genetic systems and the large number of possible starting assumptions. Nonetheless, progress is being made and current models, of which Gillespie's is an example (*Genetics*, **76**, 601; 1974), are more realistic and potentially more useful than their predecessors.

One of the main problems in models of selection is the assumption about what is actually selected. Traditionally, and in keeping with Darwinian principles, the various genotypes have been assigned fitnesses which represent their relative contributions to the next generation. The fitness differences can be the result of either differential fecundity or mortality or both. Such models, however, do not take into account many of the effects produced by different patterns of reproduction. For example, in the simplest models, there would be no difference in fitness between two individuals one of which



Alligator weed on the Georges River near the Liverpool Golf Club at Casula in November 1973. The river is almost covered by mats of the weed. Earlier spraying has proved ineffective. This matted mass of 1 million tonnes of alligator weed was swept down the river by the mid-summer floods of 1974.

had ten offspring at once and the other of which had ten offspring one at a time: the average contribution of each individual to the next generation would be the same. It is obvious, however, that there would be a great difference between them; one is investigating its reproductive effort in one clutch and the other in ten clutches. If it were certain that a clutch would survive, regardless of its size, then clearly the variability in the number of offspring of the second individual would be much smaller than that of the first.

Until the publication of Gillespie's article, selection resulting from differential variance in offspring number had been ignored by theoreticians despite its obvious importance to the evolution of complex life histories. Gillespie shows that an allele which produces the same mean number of offspring but a smaller variance will increase in frequency and he argues that an important mechanism for reducing offspring variance is repeated reproduction and smaller clutch size. Gillespie deals only with a haploid population and, even then, the analysis is somewhat difficult. His simplification of the original model certainly needs more careful examination.

Although further mathematical work on the problem is needed, other results should support Gillespie's conclusion. Although many geneticists have assumed otherwise, the evolution of complex life histories involves more than simply the maximisation of reproductive potential.

OSSO

from our Chemical Physics Correspondent
No, the title of this piece is not an acronym for the Office for Senior Scientists' Obsolescence, that secret body which arranges for its 'clients' to be shunted into administration at 35 to make way for the next generation of research workers. It is rather the genuine chemical structure of a molecule recently characterised by Lovas, Tiemann and Johnson (*J. chem. Phys.*, **60**, 5005; 1974). It is formed, under conditions controlled as much by art as science, in the fairly high pressure, 10^4 Pa (100 mm Hg), microwave discharge in SO_2 . SO is a major product and the yield of it and its dimer seems to be a function of wall conditions as well as other components in the gas mixture. Careful lifetime studies have not yet been reported, but the half life is of the order of a few seconds under the flow conditions used. Polymeric deposits formed on the walls and some OSSO appeared in the gas phase when the surface was exposed to oxygen under discharge conditions.

The identification of OSSO was by means of a microwave spectroscopic

study which established (1) that the molecule was planar; (2) that it had a large dipole moment, 10.7×10^{-30} C m (3.17 debye), parallel to the intermediate axis of inertia; (3) that alternate rotational levels were absent, being forbidden by the spin statistics of a symmetrical molecule containing the bosons ^{16}O and ^{32}S ; (4) that there was a vibrational state, probably torsional, at about 140 cm^{-1} ; (5) that an analogue containing ^{34}S could be detected and that in it the full set of rotational levels was allowed. These facts, together with the values of the rotational constants, clearly show the species to be *cis*-OSSO, planar with C_{2v} symmetry.

The geometrical structure is then established with $r_{\text{SO}} = 145.8\text{ pm}$ (1.458

Å), $r_{\text{SS}} = 202.45\text{ pm}$ (2.0245 Å), and the SSO angle $= 112.7^\circ$. This is a short S-O bond and a fairly long S-S bond so that the formula, $\text{O}^--\text{S}^+=\text{S}^+-\text{O}^-$, which matches classical valence rules, is in fact not very realistic, and the distribution of the six π electrons over the four centres is more delocalised than the above structure might imply. The characterisation of this molecule with its comparative stability is likely to catalyse further work on its electronic structure, on its vibrational and electronic spectra, and on a search for a possible *trans* form which, having no dipole moment, would not appear in the microwave spectrum. There could also be interest in isoelectronic species such as OSPF and FPPF.

Is history of science good for one?

from Robert Olby

In a recent article in *Science* (**183**, 1164-1172; 1974) the historian of physics, Brush, has described the "new look" which the history of science has acquired in recent years. Writing under the provocative title "Should the History of Science be rated X?", Brush pictures the old history of science as motivated by the search for approaches to modern scientific knowledge in the works of the past, thus to expose to view the progressive character of the development of science and its objectivity. Now the picture has changed and what Brush sees as emerging is the subjective manner in which scientific work and ideas are accepted or rejected. The roles of simplicity, analogy, unity and purpose seem to have been more important than mere empirical verification. To the believer in Galileo as the founder of the experimental method it comes as a shock to learn that the words "by experiment" were inserted in the English translation of the famous sentence "I have discovered by experiment some properties of [motion]"; or to see how the caloric theory of heat was overthrown not by the experiments of Count Rumford and Davy but by the acceptance of the wave theory of light and the analogies between light and heat.

The subjective and social features of scientific activity have been embodied in Kuhn's division of science into "normal" and "revolutionary". In a state of "normal science" the onus for proof lies with those who wish to overturn the established body of theory and practice (the

"paradigm") and not with those who uphold the paradigm. In this way the choice of problems as well as the significance accorded to experimental results tends to be determined by factors which are not purely rational and objective.

This type of approach to the history of science may be seen as subversive of the cult of scientific objectivity, so long regarded as essential to a scientist's education. Brush suggests not only that it furnishes a "more realistic picture of the behaviour of scientists", but also that it serves to soften the hard image of the "robot-like scientist lacking emotions and moral values".

Brush has, of course, expressed reservations to the "new look", he describes. He recognises that so eminent an American historian of science as Gillispie has argued for the objectivity of science. In Britain it is doubtful that an extreme relativist view of scientific knowledge has been established outside the gamut of the sociology of science. The British tend to believe that sufficient elements of such knowledge survive Kuhnian revolutions to justify the use of the words "development" and "progress". They would, at least, side with Bernard who judged progress in science by the criterion of the degree of control over the phenomena. They also recognise the distinction between what is irrational (counter to reason) and what is rational but devoid of any empirical supporting evidence. It is very doubtful that any but the most narrow-minded educators and the most gullible of students are discouraged by the historian's exposure of the rich and varied foundations upon which science has been erected.

Embryonic 'cold nose'

from a Correspondent

ANYBODY who opens a boiled egg at the blunt end will know there is an air space between the shell in this region and the rest of the egg contents. The usual explanation given for the function of this space is that it serves as a region for respiratory exchange between the embryo and the outside world; furthermore, the chick punctures the air space with its beak before hatching—a procedure which initiates respiration through the lungs and thus prepares the chick for its life outside. An additional function, which experiments on eggs of the domestic fowl and Japanese quail support, has recently been proposed by Simkiss (*J. Zool., Lond.*, **173**, 225; 1974). He argues that since loss of water by evaporation is one of the main problems associated with the development of an embryo in a closed or 'cleidotic' egg, any measure which limits such a loss would be of value.

When the parent bird is sitting on the nest the temperature of the egg and the humidity of the surrounding

air are both kept high so there is little loss of water vapour. But when the parent leaves the nest—and many birds are off the nest for periods of 5 to 15 minutes, 20–40% of the day—the temperature and humidity of the air surrounding the egg fall rapidly and, because the watery contents of the egg cool only slowly, there is a concentration gradient for water vapour to pass out of the egg; this loss of water from a warm wet body to cool dry air only stops, of course, when the parent returns or if the egg cools completely. The basis of Simkiss's argument is that the air held in the air space, because it has a low specific heat, cools rapidly when the parent leaves the nest thus reducing the gradient for the loss of water vapour through the shell. He estimates that in the climatic conditions of Britain the loss of water vapour per unit area of shell is 50% greater in those regions which overlie the liquid egg contents than in the region of the air space; with the air space region occupying about 40% of the area of the shell, he calculated a saving of about 15% during the period when a parent is not sitting.

It is, as Simkiss admits, difficult to assess whether this water-conserving

effect of the air space was more or less important in evolution than the respiratory advantages. Nevertheless, the comparative physiologist may well be able to throw light on the relative importance of the proposed functions, for one can think of climatic conditions in which some species breed but in which an air space would be of no advantage in water conservation, and species in which the egg is always kept warm by the parent.

Lasers probe the hydrogen atom

from B. P. Kibble

THE Doppler effect, which causes the apparent alteration in wavelength of the light emitted by moving atoms, has always limited the accuracy with which spectral line wavelengths, particularly those of atomic hydrogen, could be measured. But now this limitation has been overcome by saturated absorption techniques using lasers whose light can be tuned over a range of wavelengths. The first accurate measurements of a line in the hydrogen spectrum are reported by Hänsch and his colleagues at Stanford University in a recent issue

Lipmann's birthday party

from a Correspondent

THE name of Fritz Lipmann is such a commonplace in textbooks of biochemistry that many students of basic science may well be surprised to learn that, unlike Dalton and Archimedes, he is still alive and has in fact just celebrated his 75th birthday. To mark this event, eighty of his former students and colleagues attended a special symposium organised in his honour at the Max-Planck-Institut für Molekulare Genetik in Berlin-Dahlem, on July 7-9, to take part in a relaxing mixture of history, sentiment and science.

The Institut für Molekulare Genetik was an appropriate venue, for it was literally only a couple of hundred yards away that Lipmann's career really began, as an unpaid graduate student in the old Kaiser-Wilhelm-Institut in Dahlem. The institut, founded in 1910, had somehow managed to survive both the First World War and the German hyperinflation of the early 1920s, when Lipmann joined Meyerhof's laboratory there in 1927. At that time, the institut, which was of course the forerunner

of today's Max-Planck-Institut, was quite a small organisation and Lipmann and his contemporary Sir Hans Krebs gave an entertaining account of life there in the late 1920s, under the "benevolent dictatorship" of Meyerhof and Warburg, two rather forbidding characters. For instance, Sir Hans was advised on leaving the institut to take up another career, as his "chances of success in biochemistry were slight".

In 1930, Lipmann, with his wife and three years of postgraduate experience, set out for America to take up a one-year fellowship at the Rockefeller University. After that he worked for a few years in Copenhagen before returning to the United States to settle. First in Boston and later at the Rockefeller University, he proceeded to pour out his classical work on protein phosphorylation, "energy-rich bonds", coenzyme A, and a host of other topics. This diversity of interest was reflected in the scientific sessions of the symposium, in which the Lipmann alumni discussed on subjects ranging from bioenergetics to immunity in insects, and from ribosome structure to molecular biology in the reign of the Chinese Emperor Fu Hsi. The only common feature was the warmth of the tributes which



Fritz Lipmann

all the speakers paid to their former mentor. Finally a special lecture was given by Feodor Lynen of the Max-Planck-Institut für Biochemie on the isolation and characterisation of the biotin enzymes. This was the first 'Fritz Lipmann Lecture', a new event in the academic calendar, which will now be given annually in Germany as part of the programme of the Gesellschaft für Biologische Chemie, under the sponsorship of the Boehringer-Mannheim Corporation.

of *Physical Review Letters* (32, 1336; 1974), following their demonstration of the phenomenon in *Nature Physical Science* (235, 63; 1972).

In their experiment they studied the light absorbed rather than emitted by atoms. The intense light from a tuneable wavelength laser is shone on the atoms and is absorbed by a set of atoms whose component of velocity in the direction of the light enables the Doppler-shifted wavelength to be matched to their absorption. A weaker probe beam from the same laser, and therefore having the same wavelength, is made to travel in the opposite direction so it will be ignored by this set of atoms but absorbed by another set whose members have an equal and opposite velocity component. There is a special case when the wavelength is tuned to be such that the atoms which absorb the light are moving at right angles to the light paths and hence have a very small Doppler shift. Both sets then comprise the same atoms and these being partially saturated by the intense beam, absorb less of the probe beam. It is this decrease in absorption which is detected as a narrow signal without any appreciable Doppler width as the laser wavelength is tuned through the spectral line.

There is a double advantage in all this. First, the line-broadening Doppler effect, which previously blurred together the closely spaced fine structure components of the spectral line, is eliminated. Second, as this technique entails absorption of nearly monochromatic laser light the interferometer used to measure the wavelength can have a very small spectral range and a high resolving power; previously all the fine structure components were excited simultaneously in a lamp and the spectral range of the interferometer had to be large enough to encompass them all, with a consequent loss of resolution.

Hänsch *et al.* measured the absolute wavelengths of some fine structure components in the Balmer- α lines of hydrogen and deuterium to determine a value for the Rydberg constant, which characterises the wavelength of the spectral lines, and a value for the isotope shift between hydrogen and deuterium, which essentially measures the ratio of the mass of the electron to that of the proton. The accuracy achieved was an order of magnitude greater than that obtained by the emission technique.

Physicists in the past have used new techniques to measure accurately the spectrum of the hydrogen atom and in each successive instance the results have not agreed with the current theoretical description. Each consequent improvement of the theory has revolutionised physics—witness Bohr's

concept of stationary states which led to quantum theory. And again, cooling the hydrogen lamp in liquefied gases narrowed the spectral lines and revealed the fine structure which was ultimately explained by Dirac's relativistic formulation of the quantum theory. Here the requirement of negative energy states suggested the existence of the positron and brought about the science of elementary particle physics. Further minute discrepancies (Lamb shifts), confirmed by another new technique of radio-frequency spectroscopy, resulted in the quantum theory of radiation fields and particles, quantum electrodynamics (see Series, *The Spectrum of Atomic Hydrogen*; Oxford University Press 1957). Now measurements of increasing refinement can be anticipated using this latest technique of saturated absorption, particularly as what I have described is only one of a number of allied methods in which the natural resonances of atoms which give rise to their spectral lines can be explored by tuneable wavelength lasers. (One of these methods which is especially promising is two-photon absorption which has recently been demonstrated experimentally, see, for example, *Physics Today*, 27, 17; 1974.) Modern physics owes much to the exploration of the hydrogen atom at successively higher levels of precision and there is no reason to suppose that this process cannot continue.

Missing link in folding of trypsin inhibitor

from Barry Robson

A PARALLEL could be drawn between the folding of a globular protein and biological evolution in that both represent a transition from a state of disorder to one of order and function. Moreover, both processes have their missing links without which it is impossible to verify hypotheses concerning mechanism. The difficulty of finding the missing links in the folding of a globular protein is because the process is, for most proteins, approximately two state, involving unstable and short-lived intermediates which cannot normally be isolated. Three articles by Creighton (*J. molec. Biol.*, 87, 563, 579, 603–624; 1974) describe a procedure for trapping and characterising such intermediates.

As an experimental system, Creighton chooses bovine pancreatic trypsin inhibitor, a small protein of only 58 amino acid residues which inhibits the catalytic function of certain other proteins, including trypsin and chymotrypsin. The native structure of the inhibitor as obtained from living tis-

sue has been well characterised by X-ray crystallographic analysis (Huber *et al.*, *Naturwissenschaften*, 57, 389–392; 1970). As in the case of other globular proteins, the native structure is a compact, relatively rigid conformation maintained by non-covalent interactions (that is by van der Waal's, electrostatic, hydrogen bond and hydrophobic interactions), as well as by covalent disulphide bridges between cysteine residues. Trypsin inhibitor has three such disulphide bridges.

Since this compact, biologically active structure is to be the end point of the folding process, Creighton first unfolds the inhibitor in a concentrated solution of guanidinium chloride, which breaks the non-covalent interactions, and dithiothreitol, which breaks the disulphide bridges. In such conditions it is known that typical protein molecules assume highly flexible, open conformations which are, strictly speaking, not single states at all but a whole collection of conformational states of roughly equivalent energies separated by low conformational energy barriers. The importance of starting with this collection of states is that all the information for directing the folding process towards the native conformation must initially reside only in the sequence of amino acid residues characteristic of trypsin inhibitor and ultimately coded for in the chemical structure of the gene. It is therefore regrettable that the conformational disorder of the inhibitor was not actually proven before refolding, but only assumed by analogy to the behaviour of other proteins in these conditions. Although Creighton's indirect evidence for initial conformational randomness does not, however, exclude the possibility of a fairly high degree of residual conformational structure, nobody would deny that the absence of such structure is a reasonable bet which one hopes will be verified by future hydrodynamic tests.

Creighton initiates refolding of this assumed random structure by removing the guanidinium chloride by dilution and adding a disulphide reagent such as oxidised dithiothreitol. The refolding reaction is then quenched at different times by the addition of iodoacetate or iodoacetamide which stop the further making and breaking of disulphide bridges. The species so trapped at various stages of refolding are subsequently analysed by acrylamide gel electrophoresis.

When any remaining unbridged residues of the trapped intermediates are carboxymethylated, the relative mobilities of the intermediates in the acrylamide gel reveal that some contain one and some two disulphide bridges. Consideration of the time course of the appearance and disap-

pearance of these intermediates shows that the folding can be considered to occur in three steps, each associated with the appearance of a further disulphide bridge. The first step is the formation of one-disulphide intermediates which are in rapid equilibrium with each other. The rate-limiting step in their disappearance is the formation of two-disulphide intermediates which are rapidly converted by the formation of the third bridge into the biologically active inhibitor.

Those intermediates with one disulphide bridge are more closely investigated, largely because results concerning the two-disulphide intermediates are less reproducible. The most abundant species of single disulphide intermediates has a disulphide bridge between cys residues at positions 30 and 51 in the amino acid sequence, and constitutes about half the population of single-disulphide molecules. The next most abundant species has a disulphide bridge between cys-5 and cys-30, and constitutes about one quarter of the population. Two minor species, involving bridges between cys-30 and cys-55 and between cys-5 and cys-51, are also detectable.

Returning to the analogy with biological evolution, the importance of the predominating species with a bridge at cys-30 to cys-51 is that this bridge constitutes a 'living fossil' in the sense that it survives to appear in the native, folded structure. Contemporary theories of protein folding lay great emphasis on the importance of such 'living fossils'. It is widely held that local arrangements of the backbone of the protein, such as α helix and β -pleated sheet, form early during the folding but survive to appear in the native structure because of their intrinsic stability. Since none of the other detectable disulphide bridging arrangements appears in the native structure, it is interesting to consider whether the 30-51 bridge fits in with this notion. Creighton points out that in the native structure cys-30 occurs in the middle of a β -pleated sheet region and cys-51 in the middle of an α -helical region. Since the initial formation of helix and pleated sheet regions is generally supposed to be followed by mutual association, the early appearance of a bridge between cys-30 and cys-51 is consistent with the early appearance of the helix and pleated sheet features in which they occur.

A further bonus is that the early formation of the β -pleated sheet region would account for the correct threading of the backbone. Correct threading is a particular problem for trypsin inhibitor because to arrive at the native conformation the backbone must be passed through the loop formed by the 30-51 bridge. Without the initial

formation of the β -pleated sheet, it would be hard to see the factors which select for correctly threaded molecules.

Because of the emphasis on disulphide bridging it might seem paradoxical that the usefulness of Creighton's results depends on cys residues not having a special role in the folding of proteins. In fact it is crucial that disulphide bridges form only when the conformation of the molecule, determined by other factors, will permit. Hence the trapping of the disulphide intermediates is intended merely to be a device for freezing the folding process at any moment in time and it is hoped that the disulphide bridges which form are an effect, never a cause, of the conformational preferences of the intermediates. In order to satisfy this ideal it is necessary that an interaction between cys residues is no stronger than non-covalent interactions between other sidechains at the time of folding. Although the covalent nature of the disulphide bridge would seem to make this an unrealistic ideal, the disulphide bond is in fact a labile association whose stability is determined by the reducing potential of the environment. It is therefore very pertinent that, as pointed out by Creighton, trypsin inhibitor is synthesised biologically in conditions where the reducing potential actually disfavors disulphide bridge formation. Evidence summarised by Creighton would seem to suggest that cys residues are cunningly placed by nature so as to form stabilising disulphide bridges in an extracellular oxidising environment, but that they have no relevance to the normal folding process.

The most general conclusion of this work is that a non-random mixture of conformations can be formed early during the folding process, and that some of the features of the most abundant intermediates may survive to appear in the native conformation. The most important result specific to trypsin inhibitor is that the missing link from the early stages of folding is represented by the disulphide bridge cys-30 to cys-51.

Meteorites and rabbits

from David W. Hughes

THE collection of meteorites in the Australian Museum has increased enormously in the past few years, and a large portion of the new material has resulted from the activities and interests of a group of rabbit trappers who criss-cross the Nullabor Plain on motor cycles. In fact, out of 36 meteorites recovered from the plain 24 were found by the members of one family, the Carlises. The added involvement of the Kalgoorlie School of

Mines and the Western Australian Museum has increased the rate of detection of meteorites from 16 per decade, which remained constant between 1897 and 1966, to around 80 per decade since 1966.

Until the latest count (*Rec. Austr. Mus.*, **29**, 169; 1974), reported by Mason (Smithsonian Institution, Washington DC), irons formed the most numerous group of Australian meteorites. This is in marked contrast to general world statistics, in which stones predominate. A possible explanation for this is that meteoritic iron may have provided raw material for swords and ploughshares. Iron meteorites would therefore have been consumed rapidly once a native people had acquired the facility for working metal. Significantly, that facility is not possessed by the Australian aborigine. Stone meteorites, which had no practical use, were invariably worshipped. Moslem pilgrims to Mecca pay homage to the sacred black stone of Kaaba, and in Japan the Ogi meteorites were worshipped for 150 years in the belief that they were weights which had fallen from the loom of the Goddess Shokujo who lived on the shores of the Heavenly River (the Milky Way).

The problems of estimating the influx of meteorites and the ratio between stones and irons have been discussed by Nininger (*Out of the Sky, an Introduction to Meteoritics*, Dover New York; 1952) who searched for witnessed and unwitnessed meteorite falls for more than 30 years. Campaigns among rural populations in the United States were designed to acquaint farmers and ranch dwellers with the appearance and importance of meteorites. Directions were given for simple field tests to distinguish meteorites from terrestrial rocks and a price was offered for specimens as an inducement to all to keep on the lookout and report them. The programme was very successful: the number of finds increased dramatically and eventually the content of the Nininger Collection nearly mirrored the prevalence of meteorites in space (where irons make up 6% by number, stony-iron 2%, and stones 92%).

In Australia the intensive prospecting for gold and other minerals led people to expect a reasonable yield of meteorites. But, unfortunately, the prospectors avoided the flat, sandy, desert regions of the interior plains where meteorites would be more obvious. Stockmen and ploughmen may have found meteorites but, unlike the prospector, they generally had no interest in unusual rocks. On the Nullabor Plains, however, the personnel at the Kalgoorlie School of Mines have encouraged an active interest among the rabbit trappers.

articles

Nitrosoguanidine mutagenesis during nuclear and mitochondrial gene replication

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The timing of individual nuclear gene replication during S phase in an eukaryote can now be studied by nitrosoguanidine mutagenesis. Using this technique, results also suggested that mitochondrial DNA replication is synchronous and a late event in the cell cycle.

IN prokaryotes the mutagen N-methyl-N'-nitro-N-nitrosoguanidine (NG) is thought to induce mutations selectively at the DNA replication fork^{1,2} and NG mutagenesis at different stages of the cell cycle has provided information on the order and timing of individual gene replication³.

In eukaryotes, techniques do not exist for determining the ordering of DNA replication at the gene level. We have therefore tested whether NG induces mutations during DNA replication in yeast and whether the temporal ordering of replication of genes on individual chromosomes and the timing of replication of chromosomes relative to each other is feasible using the NG mutagenesis technique.

The budding yeast, *Saccharomyces cerevisiae*, is an appropriate test organism. Nuclear DNA synthesis occurs during a restricted period of the cell-cycle which can be divided into G₁, S, G₂ and M phases⁴. Yeast populations can be synchronised or fractionated according to cell age^{5,6} in the division cycle. An adequate genetic map has been developed with most of the 17 known chromosomes well marked⁷ and NG has been shown to be an effective mutagen⁸.

In addition to the nuclear genetic complement, yeast mitochondria contain mitochondrial DNA (mit DNA). Using the best available estimate⁹, each haploid cell contains about 50 mit DNA molecules. A few markers on the mitochondrial genome have been identified and progress has been made in constructing a genetic map¹⁰. The pattern of mit DNA synthesis during the yeast cell cycle has been the subject of conflicting reports. Cottrell and Avers, using *S. cerevisiae*, and Smith *et al.* with *Saccharomyces lactis*, concluded that the replication of mit DNA occurs over a restricted period at a different stage in the cell cycle to nuclear DNA replication^{11,12}. Williamson and Moustacchi, however, observed that mit DNA synthesis was continuous throughout the cell cycle in *S. cerevisiae*¹³.

If NG treatment of yeast results in enhanced mutation at the replication fork for both nuclear and mit DNA it should be possible to delineate both periods of synthesis within the cell cycle. If mit DNA synthesis is synchronous and occurs during a restricted part of the cell cycle different from that for nuclear DNA synthesis, then mutations showing mitochondrial inheritance should be induced by NG only during that part of the cell cycle.

To study the effect of NG on both nuclear and mit DNA, readily detectable forward mutations are required. Those for acquisition of resistance to antibiotics affecting mitochondrial functions are suitable because resistance to erythromycin¹⁴ or oligomycin¹⁵ can arise by nuclear- or mitochondrially-inherited mutation.

As yeast cells increase in size throughout the cell cycle and can be separated according to size by zonal rotor centrifugation, the cell cycle is represented across the rotor after centrifugation of an exponential culture.

Cell age during the cell cycle is approximately linearly related to fraction number obtained from the zonal rotor in our conditions. This was shown by measuring mean cell volumes during growth of a synchronous culture and in a different experiment in fractions obtained after zonal rotor

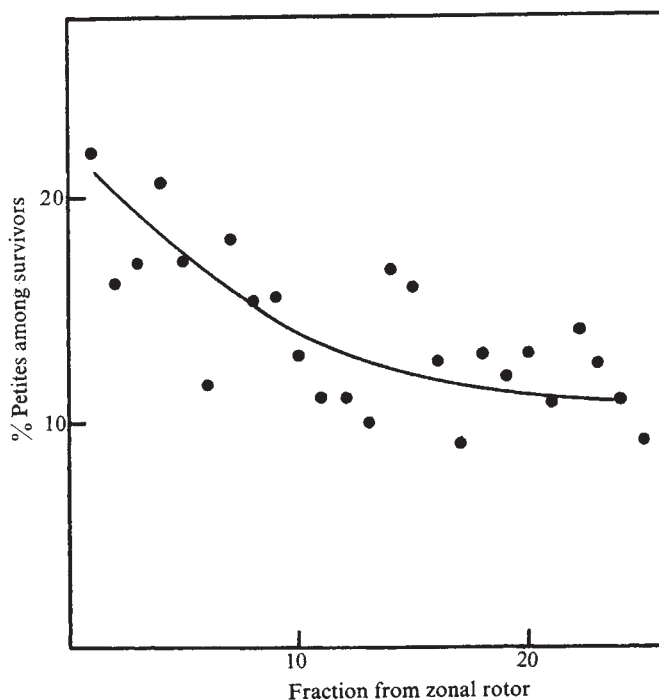


Fig. 1 Average total DNA content per cell as a function of cell age in the cell cycle. Exponential cultures of strain ID-1 grown to log phase in YEPG at 30°C were separated into fractions of various cell cycle age by zonal rotor centrifugation. For each fraction total DNA content was estimated by the Giles and Myers method²⁰ and cell concentration was determined by electronic particle counting. Fraction number from the zonal rotor is a linear function of cell age in the cell cycle.

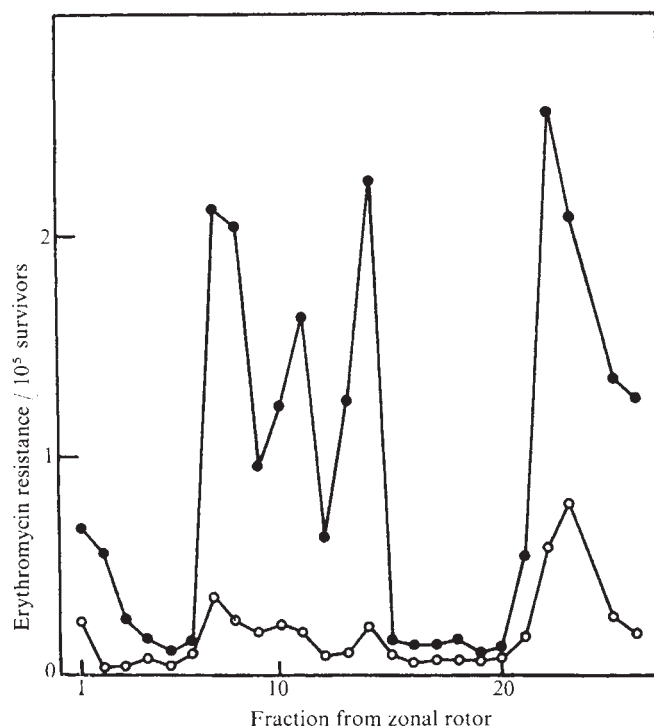


Fig. 2 NG-induced mutagenesis to ER^+ as a function of cell age. An exponential population of strain ID-1 grown to 10^7 cells ml^{-1} on YEPG at $30^\circ C$ was washed by centrifugation in sterile 0.2 M potassium acetate (KAc; pH 5.5) and resuspended in KAc containing NG (0.5 mg ml^{-1}). After 15 min at $30^\circ C$ the cells were centrifuged, resuspended in 40 ml sterile water and separated into fractions in the zonal rotor. Viable cell concentration in each fraction was determined by counting on YEPD plates. ER^+ mutants in each fraction were scored after 4 d (○) and 7 d (●) by plating between 10^6 and 10^7 survivors on to each of six YEPG plates containing $0.4\text{ mg erythromycin ml}^{-1}$.

centrifugation of an exponential population. Cell age from the synchronous culture plotted against fraction number in which the mean cell volume was identical gave a near linear curve.

Figure 1 shows the average DNA content per cell for fractions obtained by zonal rotor centrifugation of strain ID-1 growing exponentially in YEPG medium (1% yeast extract, 2% bactopectone, 3% glycerol; mean generation time: 3.5 h). As the zonal rotor separates yeast populations into fractions according to stage in the cell cycle, and the majority of DNA in the yeast cell is nuclear DNA (ref. 4), it is clear that nuclear DNA replication in ID-1 takes place mainly during the second quarter of the cell cycle, as in other strains of *S. cerevisiae*⁹.

Mutation frequency as function of cell age

An exponential culture of ID-1 growing on YEPG was exposed to NG (0.5 mg ml^{-1}) for a brief part (15 min) of the cell cycle (3.5 h) and separated into fractions according to cell age. The distribution of mutants resistant to 0.4 mg ml^{-1} erythromycin (ER^+) as a function of cell position on the zonal rotor is shown in Fig. 2. These data were plotted for mutants appearing on plates after 4 d and 7 d incubation. As similar results were obtained on plotting mutants per total cells in each fraction NG inactivation was not markedly cell cycle dependent.

NG-induced mutation to ER^+ occurred at an increased frequency in two regions of the cell cycle (represented by fractions 7–14 and 22–25 in Fig. 4). Three peaks of suscep-

tibility to mutagenesis to ER^+ (fractions 7, 11 and 14) were found in the initial period of mutant induction coincident with nuclear DNA synthesis (Fig. 1). In contrast, ER^+ mutants induced later in the cell cycle were found in a single large peak (fractions 22 and 23) in a region of the rotor containing cells close to cell division. Mutants induced in later fractions of the zonal rotor appeared earlier on selective plates than most of those in fractions 7 to 14, indicating possible differences in these two groups of mutants.

If NG acts mainly at the replication point in *S. cerevisiae*, ER^+ mutants induced in fractions 7–14 during S phase should show normal Mendelian segregation of the resistance marker from the cross to a sensitive strain. Results of the relevant genetic tests are summarised in Table 1. Most (seven of nine tested) of the mutants in fractions 7, 11 and 14 were the result of a nuclear mutation, the other two were cytoplasmically-inherited on the basis of the following criteria. First, the segregation of stable mutant and wild-type diploid cells during vegetative division of the diploid formed from a cross of the mutant to a sensitive strain; second, the tetrad ratios of 4:0 and 0:4 (sensitive:resistant) following meiosis of diploids formed in a cross with a sensitive strain; third, most ρ^- -petites derived from the resistant mutants by continuing exposure to ethidium bromide led to sensitive diploids on crossing with a sensitive strain.

By testing 16 mutants from each fraction, it was found that nuclear ER^+ mutations in fraction 14 differed from

Table 1 Characteristics of ER^+ mutants from the zonal rotor fractions

Fraction/mutant		Cross to sensitive strain Diploid phenotype*	Ascus segregation of resistance	Effect of ethidium bromide†
7	1	Mixed	4:0 and 0:4	Loss
	2	Sensitive‡	2:2	Retention
	3	Sensitive‡	2:2	Retention
11	1	Sensitive‡	2:2	Retention
	2	Sensitive‡	2:2	Retention
	3	Mixed	4:0 and 0:4	Loss
14	1	Resistant	2:2	Retention
	2	Resistant	2:2	Retention
	3	Resistant	2:2	Retention
22	1	Mixed	4:0 and 0:4	Loss
	2	Mixed	4:0 and 0:4	Loss
	3	Mixed	4:0 and 0:4	Loss
23	1	Mixed	4:0 and 0:4	Loss
	2	Mixed	4:0 and 0:4	Loss
	3	Mixed	4:0 and 0:4	Loss

* Mutants were crossed to an ER^+ strain and diploid clones tested for resistance or sensitivity to the antibiotic.

† Mutants were treated with ethidium bromide to produce petites and these were crossed to a grande sensitive strain. Diploids so formed were tested for presence or absence of resistance allele directly or after tetrad dissection.

‡ Diploids showed slight growth on selective plates.

those in the other two nuclear peaks in being completely dominant to the ER^+ allele. If the peaks in susceptibility to mutation during nuclear DNA replication represent mutation at different loci, recombination between them should be possible. Random spore analysis of the cross between haploids carrying mutations 11.2 and 14.1 (derived from the $ER^+ \times ER^+$ dissections) indicated that linkage was not detectable by this method as approximately 25% ER^+ recombinants were recovered (8 from a total of 35 spores). Analysis of the crosses of mutants derived from fraction 7 with those from 11 or 14 was not satisfactory

because of poor viability of spores and inability to disrupt tetrads in these crosses, although several ER^s spores (two out of five) were recovered from the cross 7.2 with 14.1.

Mutation to oligomycin resistance

As mitochondrial mutation to ER^r represents mutation in a restricted region of the mitochondrial genome it is important to study other mitochondrial loci distinct from those for resistance to erythromycin. Those for resistance to oligomycin, a mitochondrial ATPase inhibitor, are suitable as they are not linked to the segment of the mitochondrial genome specifying functions of mitochondrial ribosomes¹⁸.

Figure 3 shows the frequency of induction of OL^r and ER^r mutants as a function of cell age. An exponential culture of ID-1 was treated with NG, separated into fractions according to cell age and assayed for mutants resistant to either antibiotic. OL^r is induced at the same stages of the cycle as ER^r , particularly for the later part of the cell cycle in which OL^r and ER^r mutants reached peak concentration in the same fraction. During the S phase there were two main peaks of susceptibility to mutation to OL^r . These occurred within the same cell age range as those for resistance to erythromycin although in one case at least the OL^r mutation was induced in cells of different age from those for ER^r . This result is expected as the sites of action of the two antibiotics differ, erythromycin inhibiting mitochondrial protein synthesis whereas oligomycin inhibits the mitochondrial inner membrane ATPase complex. Nuclear mutations conferring resistance to one antibiotic need not necessarily confer resistance to the other.

Preliminary characterisation of the various fractions had led to the identification of cytoplasmically-inherited OL^r mutations from the late peak of mutants in Fig. 3. These

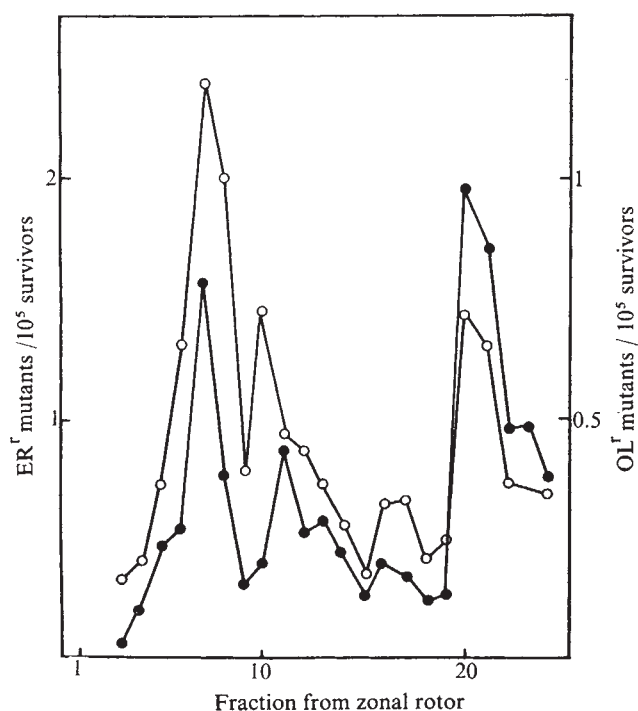


Fig. 3 Comparison between induction of OL^r and ER^r mutants by NG during the cell cycle. Experimental details were as those in the legend to Fig. 2. OL^r mutants (○) were scored after 4 d incubation at 30°C on YEPG plates containing 6 µg oligomycin ml⁻¹. ER^r mutants (●) were scored after 5 d.

were mixed with a fairly high background of nuclear mutants, in contrast with the ER^r mutants in which the nuclear region was contaminated with a low background of those of cytoplasmic origin. The majority of ER^r mutants tested were OL^s .

At concentrations similar to those used for yeast mutagenesis, NG induces up to 40% petites in *S. cerevisiae*. If this is due to a direct mutagenic effect of NG at a few specific loci, as seen in the induction of drug resistance, the fraction of petites in survivors from NG mutagenesis should

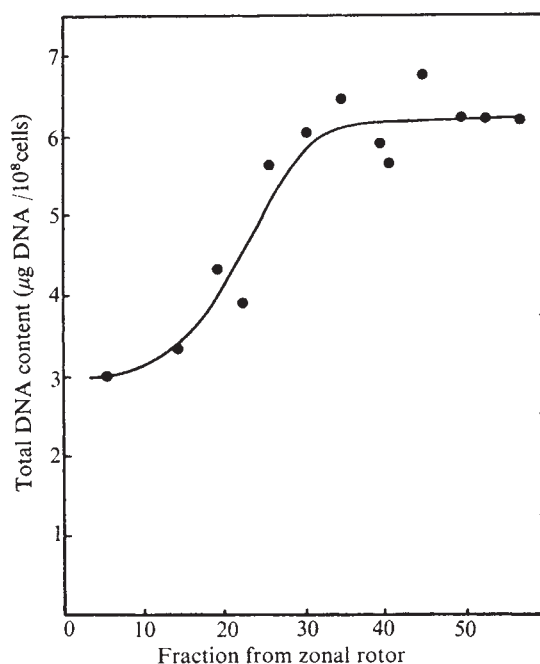


Fig. 4 Petite induction by NG during the cell cycle. Plates used for estimating viable cell concentrations in the experiment shown in Fig. 2 were used to determine the percentage of petites among survivors by the triphenyltetrazolium chloride agar overlay technique of Ogur *et al.*²¹.

show similar variations with cell age. Petites were not induced by NG in the same way as drug resistance but were found in all fractions from the zonal rotor at a frequency of 20% in young cells continuously decreasing to 10% in doublets (Fig. 4).

DNA replication and NG mutagenesis

Evidence that NG-induced mutation occurs primarily at the DNA replication point derives mainly from prokaryotic studies and is based on the observation in synchronous cultures of a correlation between the time during the cell cycle of induced reversion at a locus with its map order on the bacterial chromosome¹. Furthermore, in *Escherichia coli* and *Salmonella typhimurium*, NG induces double mutations at high frequency and these usually show close linkage².

In eukaryotes, NG-induced mutation at enhanced rates during DNA replication has been shown in *Chlamydomonas reinhardtii*¹⁷. In this system a slight increase in mutation at a cytoplasmic locus was found during chloroplast DNA replication. The results with yeast extend these observations to show that mutation at a specific nuclear locus (for example that conferring dominant ER^r) occurs only during a brief interval of the S phase, and that different loci are sensitive at different points in the S phase. We presume that

this is a result of mutagenesis in loci replicating at different times during S phase. This differential sensitivity, and its correlation with the period of nuclear DNA replication, makes it unlikely that selective NG mutagenesis is the result of changes in membrane permeability or detoxification of the mutagen during the cell cycle.

Regardless of the molecular mechanism by which NG mutagenesis is correlated with the process of DNA replication, it may now be feasible to map the temporal ordering of chromosomal replication in an eukaryote in much more detail than hitherto has been possible, as mutations in different loci replicating at different times during S phase can be resolved by zonal centrifugation.

Autoradiographic studies of a number of eukaryotes have shown that chromosomal replication follows a sequential and heritable pattern¹⁸. For example, certain chromosomes and regions of chromosomes consistently replicate late in successive cell cycles and in *Physarum* DNA replicated at a particular point in one S period is replicated at the same point in the next S phase¹⁸. Our experiments extend this observation to the level of individual gene replication. In spite of the existence of 17 chromosomes in *S. cerevisiae* and the probable existence of multiple replication origins on each chromosome, duplication of a particular locus always occurs at a fixed time in the S phase of the cell cycle since it is possible to distinguish separate peaks of NG-induced mutation at different nuclear loci after zonal centrifugation.

Mitochondrial DNA replication

Haploid yeast cells apparently contain approximately 50 circular mit-DNA molecules, each 25 μm long⁴. If NG acts selectively during mit DNA replication, the simplest interpretation of our data on coincident induction of cytoplasmic ER⁺ and OL⁺ mutations is that all copies of these two genetically distinct regions of the mitochondrial genome are replicated during the same brief interval late in the cell cycle. It is possible that all copies of the complete mitochondrial genome are replicated synchronously late in the cell cycle.

The hypothesis that mit DNA replication is periodic and a late event in the cell cycle is consistent with some biochemical data for diploid *S. cerevisiae*¹¹ and *S. lactis*¹² but differs from that of Williamson and Moustacchi who reported continuous synthesis of mit DNA in diploid *S. cerevisiae* populations synchronised by alternate feeding and starving¹³. The direct test of these alternatives will come from biochemical assays of mit DNA replication.

These discrepancies may be due to strain differences, or may result from varying approaches in studying the cell cycle. Our experiments examine a normal cell cycle as exponential cultures are treated with the mutagen and then separated according to stage in the cell cycle. Feeding and starving is a form of induction synchronisation and may not result in a normal cell cycle because artefacts resulting from metabolic disturbance and failure to synchronise all cell activities¹⁸ can occur during induction methods. Mitchison has shown the cell cycle is comprised of two cycles, the growth and the DNA-division cycles. The former is not synchronised by induction methods, and some events which normally occur periodically during the cell cycle appear continuously¹⁹.

Our results show a striking difference between petite induction and mutagenesis to antibiotic resistance. Petites were induced at all stages of the cell cycle, at a rate 10,000 times greater per survivor than mutation to ER⁺. This could be indicative of a fundamental difference between the mode of petite induction and the mechanism of mutagenesis by NG. NG is known to alter the activity of proteins²² and if as

suggested by Williamson⁹, a repression mechanism operates to regulate mitochondrial integrity, NG could act in petite induction by causing a phenotypic alternation in the activity of a repressor. This would be distinct from a mutagenic process as is the induction of petites by 5-fluorouracil⁹.

It is frequently difficult to demonstrate activity of mutagenic compounds in induction of mitochondrial mutation. The recovery of a peak of mitochondrial mutants at late stages in the cell cycle following NG treatment indicates that this compound is an effective mutagen for the mitochondrial genome.

NG mutagenesis, in conjunction with techniques for separation of populations according to the stage reached in the cell cycle provides a powerful selective technique for enrichment of particular mutants, and the ability to 'direct' mutagenesis discussed by Cerdà-Olmedo *et al.*¹ may now be possible in eukaryotes.

NG induces mutations conferring resistance to antibiotics affecting mitochondrial function at two stages of the cell cycle. One stage is coincident with nuclear DNA replication while the other is late in the cell cycle and may be that at which mitochondrial genes are replicated. A particular nuclear gene is susceptible to NG mutagenesis only at a specific time during S phase and different unlinked nuclear genes are sensitive at different times during S phase. NG is presumed to act during gene replication, and it should therefore be possible to determine in yeast the temporal pattern of chromosomal replication at the gene level.

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Educability and group differences

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Professor Jensen replies to criticism of his book Educability and Group Differences made by Professor J. M. Thoday in a review published in Nature.

I WISH to reply to the two main points of criticism made in the review of my book, *Educability and Group Differences*, (Methuen, London, 1973) by Professor J. M. Thoday in *Nature* (245, 418-420; 1973).

I had reported that when white and negro children were matched for a particular IQ score, say 120, the siblings of the two racial groups differ in average IQ, and that the difference is consistent with the phenomenon known as 'regression to the mean'. The white siblings regress toward the white population mean IQ of 100, the negro siblings toward the negro population mean of 85. The amount of regression is predictable in both racial groups from a genetic model in which the genetic correlation between sibs is 0.05 and the heritability, h^2 , of IQ is 0.80. The same model, using different empirically estimated values for h^2 , is applicable to any other continuous traits, such as height, weight, and fingerprint ridges. (In the present example, approximately the same amount of sibling regression was found for height as for IQ, and the same equation predicts as well for negroes as for whites.) All these findings are consistent with an already existing polygenic model which has proven theoretically valuable in understanding variation in metrical characteristics, physical and behavioural.

Factor X

But Thoday claims that a finding such as I reported "... adds nothing whatsoever to the strength of the genetic hypothesis" on the ground that the evidence is also as compatible with an explanation in terms of a hypothetical environmental "factor X" as in terms of the genetic hypothesis. But "factor X" is, of course, a purely *ad hoc* hypothesis. No previous environmentalist theory or model has been put forth which would have predicted the quantitative aspects of these findings, nor the linearity of regression throughout the middle 98% of the IQ range, nor the similarity of regression for IQ, height, and weight, nor the fact that the same regression equation works equally well for both racial groups. All these points, which are consistent with a much larger body of genetical theory and findings applicable to all organisms, would have to be regarded as coincidences in terms of the purely *ad hoc* hypothesis that some as yet unidentified environmental "factor X" is responsible. The findings, of course, cannot prove or disprove any *ad hoc* hypothesis which is invented expressly to explain them. But the fact that they are consistent with a genetic model which is not *ad hoc* is a point in favour of the genetic explanation. Philosophers of science, I believe, would support my contention. In fact, a forthcoming article, "Progress and Degeneration in the IQ Debate" by Dr Peter Urbach (*Br. J. Phil. Sci.*) argues that the chief weakness of the environmentalist position is its extreme recourse

to *ad hoc* explanations, often mutually inconsistent, of findings which were predicted by, or which easily fit into the framework of, already existing genetical theories supported by a growing internally-consistent network of evidence.

Thoday's second criticism is intended as an example of uncritical acceptance by me of some evidence which seems to favour a genetic hypothesis.

It involves my reference to a published study by DeLemos, which shows that a sample of full Australian aboriginals performed significantly less well on several of Piaget's tests of conservation than did part aboriginals (with the average genetic equivalent of one Caucasian greatgrandparent), despite the fact that the two groups shared much the same general environment without any distinguishable systematic environmental differences between the full and part aboriginals. Since the Piagetian tests, which are intended to reflect changes in mental maturity, are sensitive to age differences, and DeLemos's subjects ranged in age from 8-15 yr, Thoday conjectures that the findings reported by DeLemos could be an artefact of her not having controlled for age. The much more detailed presentation of the data and other analyses in DeLemos's PhD thesis (460 pages), of which I obtained a microfilm copy in 1967 and on which her later published article was based, however, shows that Thoday's statement that "the data cannot be regarded as demonstrating that the ancestry difference has significant effects" is not borne out by the evidence. Nor did I notice any other likely artefacts in my reading of DeLemos's thesis. My personal discussion of this research with Dr DeLemos, in 1969, added to my confidence in her conduct and analysis of the study.

Partial correlations

The invalidity of Thoday's conjecture can be demonstrated perhaps most simply by a reanalysis of the original data provided by DeLemos, using partial correlations. I have performed this analysis, based on all 80 subjects from the Hermannsburg group (42 full and 38 part aboriginals) ranging in age from 8-15 yr. Intercorrelations were obtained between age in months, the exact percentage of Caucasian ancestry, and total score on the six tests of conservation (each test scores as 0, nonconservation, 1, transitional; 2, conservation). The zero order correlations among these variables are: age $\times$ %Caucasian ancestry: $r=0.192$ ($P<0.05$); age $\times$ total conservation score: $r=0.350$ ($P<0.01$); %Caucasian ancestry $\times$ total conservation score: $r=0.478$ ($P<0.01$). If the correlation between ancestry and conservation score depends upon the correlation of each of these variables with the third variable, age, for example, then the partial correlation between ancestry and conservation, with the effect of age statistically held constant, should be reduced to a value not significantly greater than zero. If, on the other hand, the partial correlation is significant, it means that ancestry makes some contribution to the conservation score independently of age. The partial correlation between Caucasian ancestry and conservation score turns out (independent of age) to be 0.448, which is significantly greater than zero at the 1 % level of confidence. A more

complex type of analysis (ANOVA of total conservation scores, with ancestry nested within 1 yr age groups), too involved to present here but which does not make any assumptions about linearity of regressions as is implicit in partial correlations, fully supports this conclusion that DeLemos's finding is not attributable to age differences between the full and part aboriginals. Also, it can be shown that the sex of the subjects has no significant relationship to any of the other variables in DeLemos's study.

The fact that another study of conservation in full and part aborigines, by Dasen (published in 1972, after my citation of the DeLemos study was in press), failed to find a significant relationship between ancestry and conservation

performance does not automatically invalidate the DeLemos study, which appears methodologically at least as sound as the Dasen study. The latter involved certain procedural and sampling differences, so that it cannot be regarded as a true attempt at replication of the DeLemos study. Dasen's discrepant findings do mean, however, that the findings by both DeLemos and Dasen are not clearly understood in terms of the procedural variables affecting performance and that neither's results are generalisable to the general population of aboriginals or to other tests of conservation. The only answer for this state of affairs, which is of course a common occurrence in empirical research, is to systematically pursue further investigations in the same vein.

letters to nature

Absence of soft X rays from Eta Carinae

THE X-ray telescopes on OAO-Copernicus have been used to search for X-ray emission from η Carinae. The instrumentation has been described elsewhere¹⁻²; briefly, it comprises two paraboloidal X-ray telescopes operating in the energy ranges 0.5–1.5 and 1.5–4.6 keV, with a separate collimated proportional counter operating from 2.5–7.5 keV.

The energy source of η Car, first seen in the optical spectrum³ and now in the infrared⁴, is not yet entirely clear^{5,6}. Thackeray⁵ suggested that it belongs to a new, slow class of supernovae associated with the birth of an expanding stellar association, and Ostriker and Gunn⁷ have developed a supernova model of large mass ($\approx 50M_{\odot}$) energised by a central neutron star and emitting synchrotron radiation from the surrounding nebulae in the optical and infrared⁸. Alternatively⁶, the object may be a very massive star ($600\text{--}100M_{\odot}$) which is vibrationally unstable and has ejected a fraction of a solar mass to form the observed nebulae and condensations⁹; or it could be a very young massive star approaching the main sequence^{3,6}. On either of these last two hypotheses the radiation is entirely thermal: the optical continuum results from a hot central star or from two-photon emission from metastable hydrogen, and is distorted by reddening in a circumstellar dust cloud¹⁰ which re-emits the absorbed radiation in the infrared^{11,12}. The thermal model, more probably involving a hot central star, is strongly supported by the relative intensities of emission lines of hydrogen¹³ and permitted¹⁴ and forbidden¹⁰ FeII, by the detailed analysis of Davidson¹⁵ and by the presence of silicate bands near $10\text{ }\mu\text{m}$ (ref. 16); but measured intensities of [S II] lines do not show the expected intrinsic reddening¹⁷.

On the synchrotron model, inverse Compton scattering may lead to an observable X-ray flux¹⁸, which would probably be accompanied by intense synchrotron X rays if the 'pulsar' mechanism were operative. On either model the observations of an expanding shell moving out into the surrounding medium must imply the presence of a shock wave with compression and heating of the ambient gas to a temperature at which the emission of X rays becomes important. An observation of η Car in X rays would therefore be of great value in helping to decide between the two models and in setting constraints of the physical parameters involved.

A soft X-ray source found in a scanning rocket experiment¹⁹ was located somewhere near the galactic equator and within 0.3° of the galactic longitude of η Car, with which it was tentatively identified. This unconfirmed identification led Davidson and Ostriker²⁰ to comment on the parameters of the thermalised shock front which precedes the expanding shell and which was assumed to account for the X rays observed below

2.7 keV. They concluded that the shell must be moving into a surrounding medium of density $\sim 2,000\text{ cm}^{-3}$, which was rather difficult to account for, because it implied that η Car had not cleared a cavity around itself by mass outflow before the large outburst of 1843. Another possible consequence of this model is that the green coronal line [FeXIV] λ 5,303 may be present in the visible spectrum²¹. A spectral tracing from the Radcliffe Observatory indicates that this line, if present at all, is considerably weaker than predicted, but this negative result cannot be treated as a very conclusive test of the shock model. The pulsar model seems, on the other hand, to have been ruled out by the steep slope and modest intensity of the observed X-ray flux²⁰, even if the identification¹⁹ with η Car were correct.

Eta Car was observed by the X-ray telescopes on board OAO-Copernicus on May 25, 1973. Both telescopes used the largest field of view (equivalent beam width 12 arc min) and were pointed 'on' and then 'off' the source for six sets of observations of about 14 min each. The slew 'off' the source was of about 5° in range, and provided a reliable background estimate. No statistically significant difference in count rate was observed in either telescope, which leads to the upper limits (at the 2σ level) shown in Table 1. Similarly, no significant count rate was

Table 1 Upper limits to the X-ray flux from η Carinae

Energy band (keV)	0.5–1.5	1.5–4.6	2.5–7.5
Total count rate (s^{-1})	<0.01	<0.13	<0.025
Maximum energy flux in band erg $\text{cm}^{-2}\text{s}^{-1}$	$1.6 \times 10^{-11*}$	$4 \times 10^{-11*}$	$2 \times 10^{-11\dagger}$

* Assuming thermal spectrum¹⁷ $kT = 0.26\text{ keV}$, and hydrogen column density $N_H = 3 \times 10^{21}\text{ cm}^{-2}$

† Assuming a synchrotron spectrum, $\alpha = 0.8$ (ref. 16).

recorded in the collimated proportional detector, which has a 3° field of view; the corresponding upper limit (Table 1) is slightly below the threshold of the third Uhuru catalogue of X-ray sources²², which is $3.4 \times 10^{-11}\text{ erg cm}^{-2}\text{ s}^{-1}$ (2 Uhuru units) over the energy range 2–6 keV. An upper limit to the X-ray luminosity L_x of the source, between 0.5 keV and 7.5 keV can be obtained by removing the assumed effect of a column density $N_H = 3 \times 10^{21}\text{ cm}^{-2}$ on the maximum flux observed in the 0.5–1.5 keV band and extrapolating the continuum to higher energies. Assuming a distance of 2 kpc, this gives $L_x < 2 \times 10^{34}\text{ erg s}^{-1}$; the result is approximately the same whether the thermal ($kT = 0.26\text{ keV}$) or synchrotron ($\alpha = 0.8$) spectrum is assumed, and does not vary significantly for N_H values between 2.5 and $4.8 \times 10^{21}\text{ cm}^{-2}$. The interstellar cross sections used here are those of Brown and Gould²³.

The low energy flux (0.5–1.5 keV) is at least an order of magnitude below that expected from the Livermore source.¹⁹ Possible explanations for this disparity are:

- (1) that the source found by Hill *et al.*¹⁹ was not η Car but was instead a soft source some distance away in galactic latitude;
- (2) that the observed emission¹⁹ came from an extended region around η Car at least 1° in diameter
- (3) that the X-ray flux from η Car is variable.

In the second case the low energy flux within the field of view of our telescopes would have been undetectable, and at high energies the source was not detected in either of the two experiments. The existence of such an extended source seems very unlikely, however, in view of the optical morphology of the region: η Carinae is embedded in Herschel's 'Keyhole Nebula' NGC3372, and there is no evidence for any extended supernova remnant. The third possibility also seems very unlikely if the X rays come either from a shock region outside the $10''$ visible shell or from the volume inside the shell. We can see no observational evidence for any variable source with a time scale of the order of 1 min over 40 min of observation; a source as strong as that found by the Livermore group¹⁹ would have been observed in a few minutes.

We shall therefore assume that the first hypothesis is correct. The present upper limit on soft X-ray emission then removes the problem encountered by Davidson and Ostriker²⁰ of a high ambient density around the object, and it also removes any basis for expecting coronal lines in the visible spectrum. The pulsar model, already unlikely on the basis of the Livermore observation²⁰, now seems even more unlikely, because the total X-ray luminosity which, on the basis of Ostriker and Gunn's model⁷, should exceed that of the Crab Nebula ($\sim 10^{38}$ erg s⁻¹ above 1 keV), is at least three orders of magnitude lower. On the Compton model¹⁸, the predicted flux density in the neighbourhood of a few keV is of the order of 10^{-28} erg cm⁻² s⁻¹ Hz⁻¹ for the 'most likely' model with relativistic electrons with a low energy cut off at $\gamma = 10^3$ and a magnetic field of about 10^{-3} gauss, but it can be very much less if the cutoff energy is greater. The corresponding upper limit from our observations (averaging 1.5–7.5 keV) is 4×10^{-29} erg cm⁻² s⁻¹ Hz⁻¹, which could be taken as indicating a higher low energy cutoff on this model.

The balance of the evidence, however, reinforced by the failure to detect any X rays, favours strongly the view that the spectrum of η Carinae is of thermal origin, with the bulk of the energy coming out from dust grains.

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Radio emission from Hen1044

CONTINUUM radio emission has been detected from several early-type emission-line objects which show a strong infrared excess¹⁻⁹. Here we report the detection of radio emission from a Southern Hemisphere compact emission-line object Hen1044 (He2-113).

Observations were made at 3.0 and 6.0 cm using the CSIRO 64-m telescope at Parkes, which has half-power beamwidths of $2'.5$ and $4'.0$ at these two wavelengths. At both wavelengths beam-switching was used to reduce atmospheric effects, the beam separations being 6.2 and 2.8 half-power beamwidths respectively. At 3.0 cm (9.86 GHz) a mixer receiver¹⁰ was used with a predetection bandwidth of 500 MHz and a system noise temperature of 650 K. At 6.0 cm (5.0 GHz) a cryogenically cooled parametric amplifier was used with a predetection bandwidth of 300 MHz and a system noise temperature of 80 K. An on-on source technique of observing similar to that described previously¹ was used, except that here the two beams were separated in azimuth.

Radio emission was detected from Hen1044 at both 3.0 and 6 cm wavelengths. The flux density determined from 10 independent measurements made during the period 1973 August 24 to 27 was 0.24 ± 0.03 Jy at 3 cm. Observations at a wavelength of 6.0 cm were made during the period 1973 October 17 to 22. Two independent measurements yielded a flux density of 0.11 ± 0.03 Jy. Scanning observations were also made at this wavelength. The means of five right ascension scans and 11 declination scans are shown in Fig. 1. The radio source is unresolved and the region is reasonably free of confusion. The differences between the

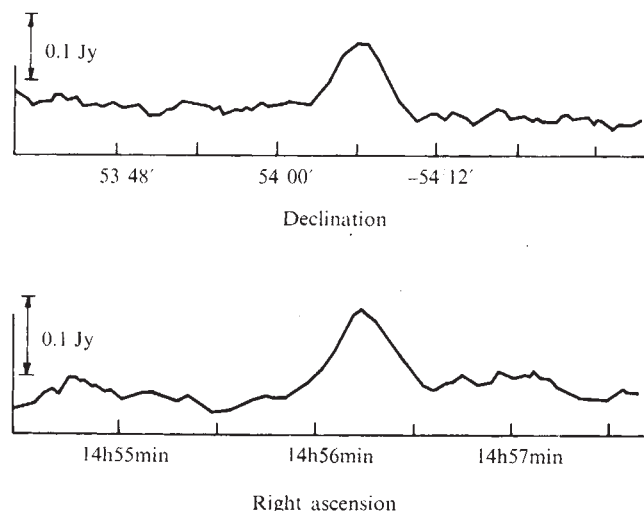


Fig. 1 Declination and right ascension scans of Hen1044 at 6 cm; the epoch for both coordinates is 1950.

optical position (RA 14 h 56.3 min dec. $-54^{\circ}06'$, epoch 1950) and the radio position are 4 s in right ascension ($36''$ on the sky) and $20''$ in declination. These differences are within the pointing errors of the telescope.

The object Hen1044 has a stellar appearance¹¹, with "no obvious surrounding nebulosity"¹². Its optical spectrum, which has shown no appreciable change between 1962 and 1973 (refs 12,13), is that of a low-excitation planetary nebula associated with a cool WC star. The object is one of only four which have been classified¹² as WC 10. Continuing mass outflow is indicated by the presence of P Cygni profiles. These characteristics are suggestive of an embryonic planetary nebula. Hen1044 is very similar to the WC 9 object HD167362, from which radio emission has recently been detected^{5,14}.

The continuum radio spectrum of Hen1044 is not well defined by the two flux density measurements reported here. But if it is assumed that the radio emission did not vary significantly between the two dates, and that the emission is produced by the bremsstrahlung mechanism, then the emitting region has an optical depth of 1 at ~ 8 GHz, indicating an emission measure of $\sim 10^8$ cm⁻⁶ pc. If the radio emission is associated with circumstellar gas at a temperature $\sim 10^4$ K, then the angular size of the radio source is $\sim 1''$, consistent with the upper limit to the optical size. Very similar results have been found¹⁴ for the bright central component of HD167362.

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marily from extragalactic sources. In an intermediate group there are those³ who think that perhaps only the most energetic particles ($E > 10^{18}$ eV) are derived from extragalactic sources.

The observation^{4,5} of cosmic γ rays has given hope for a distinction between the Galactic and extragalactic models, at least for the energies of cosmic ray protons ($1 \text{ GeV} < E < 10 \text{ GeV}$ mainly) whose collisions with interstellar gas atoms are considered to give rise to the π^0 mesons from which the γ rays are derived. The experimental data, which relate to the intensity of γ rays above 100 MeV as a function of Galactic longitude, indicate rather clearly that there is an increase in the emissivity of γ rays (defined as the rate of production per unit volume) towards the Galactic centre (GC) with a peak in the region of radial distance from the GC, R , of about 5 kpc. There is some argument as to the actual variation of emissivity with R : Puger and Stecker⁶ derive a very sharp peak at $R=5$ kpc whereas one of the present authors, Strong⁷ (to be published) derives a rather more gradual variation of emissivity. Figure 1 shows

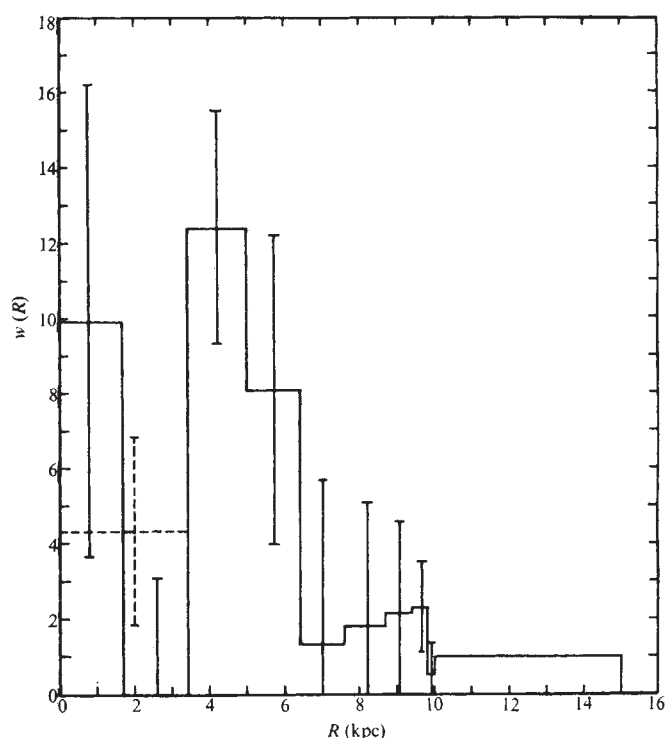


Fig. 1 The variation of γ -ray emissivity relative to that at the Sun $w(R)$, as a function of distance from the Galactic centre (R), deduced from observations by the OSO-III and SAS-II satellites. Cylindrical symmetry about the centre has been assumed in order to unfold the experimental data. The quoted errors are statistical only. — — Average emissivity for the first two bins of radial distance.

the average relative emissivity derived by the present authors using Strong's method for the longitude range 270° – 90° .

So far the interpretations have suggested that there is an increase in the flux of cosmic rays towards the GC corresponding to cosmic rays of Galactic origin. A number of models have been proposed: an increased containment time arising from an enhanced magnetic field⁷, structured acceleration in the hydrodynamic shock driven by the expanding gas in the "3 kpc arm"⁸ and, very recently, an increased yield in the spiral arms resulting from an assumed correlation between the cosmic ray flux and the neutral hydrogen density in the arms (Bignami and Fichtel¹⁵).

In all these models it is assumed that the predominant interaction responsible for the parent π^0 mesons is between

Relevance of cosmic gamma-rays to origin of the cosmic radiation

THE controversy over the question of the origin of energetic cosmic rays is well known. There are those who believe that the bulk of the radiation comes from Galactic sources, such as supernovae¹ and others² who find rather good reasons for supposing that the radiation comes pri-

cosmic-ray protons (with a small admixture of α particles) and the protons from neutral hydrogen atoms. The variation of atomic hydrogen density with R has been derived from 21 cm data which shows (see Mezger⁹ for example) that the average surface density of neutral hydrogen in the range $0 < R < 5$ kpc is about one half that at $R \sim 10$ kpc (the location of the Solar System). In all the calculations some allowance has been made for the presence of unseen gas, presumed to be mainly molecular hydrogen, by multiplying the predicted γ -ray yields by a factor of ~ 1.5 , this having been thought to be a 'reasonable' factor.

It has been noted before that the distribution of γ -ray emissivity appears to correlate quite well with that of giant H II regions (ref. 8 and A. W. Strong, unpublished). Now it is well known that dense ($\sim 10^3$ cm⁻³), massive ($\sim 10^4$ – $10^5 M_\odot$) molecular clouds are found in association with such H II regions¹⁰, and such clouds will be copious sources of γ rays. (The possibility that nearby clouds may be observable as point sources has in fact been suggested by J. H. Black and G. G. Fazio, unpublished). What appears not to have been realised until recently is the fact that the contribution of the molecules to the gas density at $R \sim 5$ kpc may be very large: according to Solomon¹¹ and N. Z. Scoville and P. M. Solomon (private communication), the smoothed molecular hydrogen density in the region 4–6 kpc from the Galactic centre may be as high as 10 cm⁻³, compared to a total gas density near the Sun of only about 1 atom cm⁻³. (It should be remarked that the importance of the correlation between the molecular hydrogen distribution and that of γ rays has also been stressed recently by Solomon and Stecker¹².)

As is clear from Figure 1, the increase in molecular hydrogen density is quite adequate to account for the observed γ -ray intensities with a uniform cosmic ray flux if, as would seem likely, the molecular clouds have a distribution perpendicular to the Galactic plane not too different from that of the H II regions (with a full width of about 100 pc¹³). Explanation in terms of molecular hydrogen was in fact suggested some time ago by Stecher and Stecker¹⁴, although at that time there was no direct evidence for an increase in the molecular hydrogen density towards the Galactic centre and later explanations by Stecker and coworkers have concentrated on cosmic-ray gradients such as would result from Galactic sources of the cosmic-ray protons or at least Galactic acceleration of the particles.

The importance of the new result is that the necessary constancy of the cosmic-ray flux would be more consistent with a largely extra-galactic origin of the cosmic rays rather than a Galactic one.

In conclusion, it is clear that, unless the molecular hydrogen measurements are seriously in error the γ -ray data do not now necessarily demand explanation in terms of a Galactic origin for the initiating cosmic rays.

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Formation of holes in the solar corona

SOFT X-ray spectroheliograms obtained from Skylab¹ and rocket flights² show many bright filamentary features which map out the magnetic structure of the solar corona. Additional interesting features are the extensive regions from which the emission is extremely low. These long, but relatively narrow, 'coronal holes' can stretch much of the way across the solar disk in a roughly N–S direction. The photosphere and chromosphere beneath are relatively featureless and have low magnetic flux density. The magnetic structure of these lower levels is not untypical of other quiet regions on the Sun where coronal holes have not developed. This suggests that the magnetic configuration associated with the holes might not have emerged from the solar surface with any particularly unusual geometry, but this might have developed later due to some rearrangement within the atmosphere. Changes in field structure within the corona have been regarded for more than a decade as part of the normal process of development during the solar cycle³.

The spectroheliograms indicate the existence of long magnetic-arch structures in the solar atmosphere². It is thought that these arches are produced by merging of smaller structures by cross-connection of field lines, since this results in a reduction of the magnetic energy stored³. How this proceeds depends upon the initial conditions, but the trend is illustrated by the simple case in Fig. 1a. Where the flux tubes touch their neighbours there will be merging to produce the resultant fields shown as solid curves with double arrow heads. Even when the initial conditions are more complex, as when the original arches emerge from the solar surface at different times, the trend should be the same.

Magnetic arches have a preferred alignment on the Sun⁴. In the northern hemisphere the vertical flux tubes tend to lie within NE–SW planes, while south of the equator they stretch roughly SE–NW. (Hereafter, both these directions are denoted as E–W. The description can then remain reasonably general because it is unnecessary to specify which hemisphere is being considered.) At any time the field tends to point from E to W in one hemisphere but from W to E in the other. In both cases the sense reverses between one 11 yr cycle and the next.

The situation discussed so far concerns interaction between the relatively young flux tubes developing within

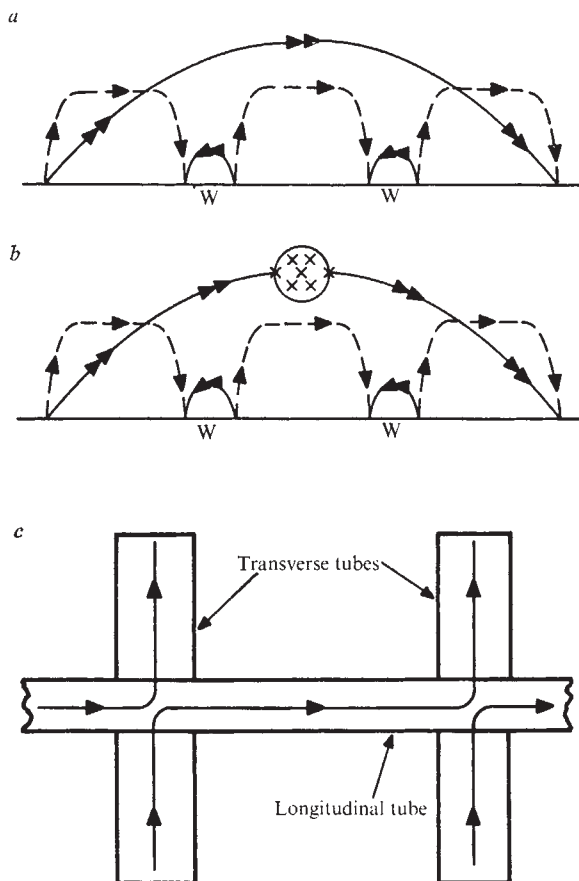


Fig. 1 Each dashed curve represents a magnetic flux tube which passes from the photosphere into the solar atmosphere (presumably related to development at supergranulation.). Because these arches have similar polarities they can merge to reduce the magnetic energy. *a*, The solid curves represent the resultant flux tubes; *b*, the situation when an additional flux tube crosses the region perpendicular to the plane of the paper. The resultant solid curve merges with this new tube. The short resultant loops produced at the regions marked *w* will possibly be carried away³ by the flow of material at the solar surface. In *c* the horizontal flux tube shown in *b* is seen to cross two parallel arches. Curves with arrow heads illustrate how cross connection between field lines from each of the three flux tubes allows a line to pass from one transverse arch to the other.

quiet regions on the Sun. It is necessary to take into account the interaction with other arches produced earlier in the solar cycle, or even during the previous cycle. Some particularly long structures develop in roughly N-S directions. These stretch between pairs of active regions or from active regions to polar caps⁵. It is also possible that flux passes from one pole to the other³. If one of these N-S flux tubes comes into contact with the E-W arch system forming in Fig. 1*a*, merging between the perpendicular fields can proceed⁶. A section through the new system is shown in Fig. 1*b*; the plan view of this structure (Fig. 1*c*) shows how a field line from one of the transverse arches might cross to another by passing along a length of longitudinal flux tube. Cross coupling of field lines which leads to this configuration can be expected because it reduces the magnetic energy stored in the whole structure.

The situation becomes particularly interesting if some of the transverse arches have polarities opposing the others. A simple system containing a pair of arches illustrates this in Fig. 2*a*. A field line crossing between the pair now has both feet to one side of the longitudinal flux tube, so that the relaxation accompanying merging can separate it from the original structure. If cross connection between the pair of arches became complete, a cavity would be

produced in the magnetic field, as shown in Fig. 2*b*. The flux along the N-S tube gets 'eaten away' in this process.

Figure 2*b* shows the simplest situation where a pair of neighbouring antiparallel arches merge together. In practice the horizontal flux tube will cross many arches so that all the field lines from one will be unlikely to pass into a single antiparallel structure. A cavity can be produced nevertheless if the transverse arches towards one end of the N-S flux tube have one polarity, while the other end makes contact with fields of reverse polarity. A formalised representation of this appears in Fig 3*a*. (Field lines like that in Fig. 1*c*, which cross from one arch to a parallel one on the same side of the boundary, have not been included because these do not represent a state having minimum energy. Such lines continue to interact with flux lying N-S until antiparallel arches are linked). This is just the situation which can produce very long coronal holes if the N-S flux tube is suitably located on the solar disk. Two cases are of interest:

(a) The more obvious case is the one where the longitudinal flux tube crosses the solar equator in the manner of the 'trans equatorial arches' observed by Hansen *et al.*⁵. It has been pointed out already that E-W arches crossing this tube would change polarity across the equator. The general alignment of coronal holes in the N-S direction between hemispheres can therefore be explained in this way.

(b) A stage is likely to be reached at the transition between solar cycles when antiparallel magnetic arches form in a single hemisphere. As solar minimum approaches, polarities associated with the old 11-yr cycle are found near the equator, while reversed fields due to the developing cycle form at intermediate latitudes³. Suitable conditions seem to be developing at present since Gillespie *et al.*⁷ reported the appearance of new cycle polarity configurations during August 1973.

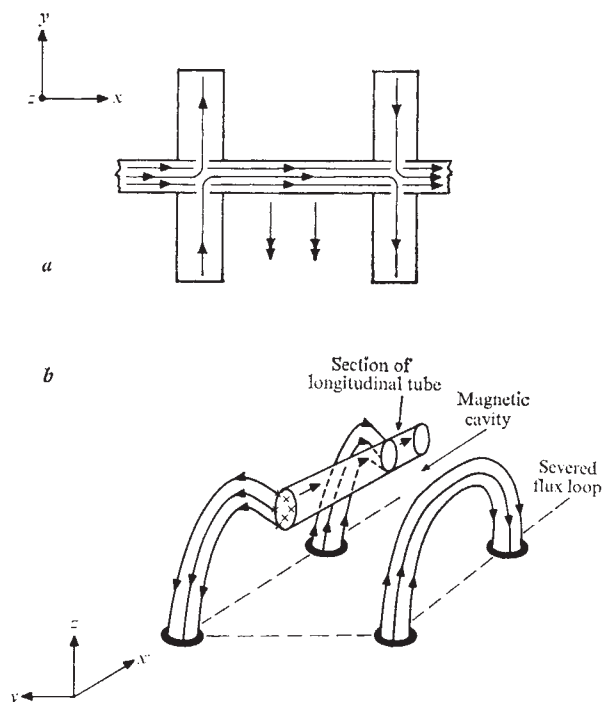


Fig. 2 *a*, is similar to Fig. 1*c*, except that the fields along the transverse arches are now antiparallel. A field line crossing from one of these to the other should relax, in the direction of the double-headed arrows, from the position shown. *b*, The extreme case when all the field lines from one arch pass into the other.

At the stage when the old and new 11-yr cycles are both active, the polarities of arches will change between zones as indicated in Fig. 3b.

In addition to the coronal holes, soft X-ray spectroheliograms show regions of low emission which form along the path of dark filaments (prominences) observed in H α spectroheliograms. One of these filament cavities is labelled in Fig 1 of ref. 1, while several good examples (one of which is Y-shaped) are seen as long thin dark features in Fig. 1 of ref. 2. Such structures could be closely related to coronal holes since there is evidence that dark filaments might have the magnetic configuration drawn in Fig. 1c. It has been suggested⁸ that condensed material is embedded in a longitudinal field produced by local

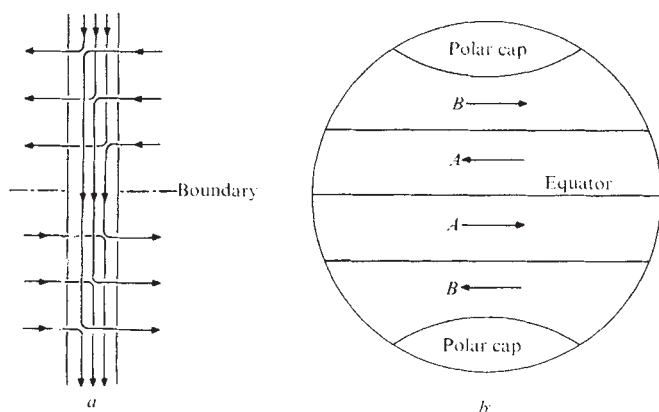


Fig. 3 The situation shown in Fig. 2 is unlikely because it assumes that all field lines pass from one arch to a second neighbouring structure. It is far more probable that there would be interaction between numerous arches crossed by the horizontal flux tube. This could still lead to the formation of a cavity, however, if the transverse arches had different polarities on each side of a boundary. *a*, A formalised representation of how field lines from one or more transverse arches on one side of the boundary can pass into one or more structures of reversed polarity on the other side. *b* shows a number of boundaries on the solar disk across which changes in polarities of arches are likely to occur. The arrows show field directions at one stage during a 22-yr cycle. Regions denoted by *A* have fields associated with the first half of this cycle while regions *B* have polarities of the second half-cycle.

shearing of transverse support arches. Even if such structures are not formed by the exact sequence of events described here, it is still possible that a reversal in the polarity of the support arches along the length would lead to the formation of a cavity.

In the model outlined the flux tubes need only merge on a time scale of the order of one day, over which period changes in the structure of coronal holes occur. Such a rate of merging appears acceptable on theoretical grounds although, as Sweet⁹ points out, it is difficult to explain the far more rapid changes needed to account for solar flares.

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Ionospheric effects of the Flixborough explosion

ON June 1, 1974, an explosion of unprecedented magnitude occurred at the Nypro plant at Flixborough, Lincolnshire. A considerable blast wave was produced and evidence is presented here to show that this wave penetrated the atmosphere to ionospheric heights. Our purpose is to report these major ionospheric disturbances since they may yield information regarding the time sequence of the explosion and the amplitude of the blast wave that it created.

Naturally occurring waves in the ionosphere have been studied at Leicester using the high frequency (HF) radio Doppler sounding technique¹. In this method an HF radio-wave is reflected from the ionosphere at steep incidence and the frequency of the received signal is monitored². Acoustic-gravity waves propagating through the atmosphere displace the reflection point and a Doppler frequency shift is produced in the reflected signal. The magnitude of the Doppler shift Δf is proportional to the rate of change of phase path of the radiowave according to the expression

$$\Delta f = -(f/c)/(df/dt) \quad (1)$$

where f is the radiowave frequency and c is the velocity of light. If three spaced reflection points are available then the speed and direction of the disturbance may be determined from the time delays in the Doppler frequency changes observed on the three transmissions.

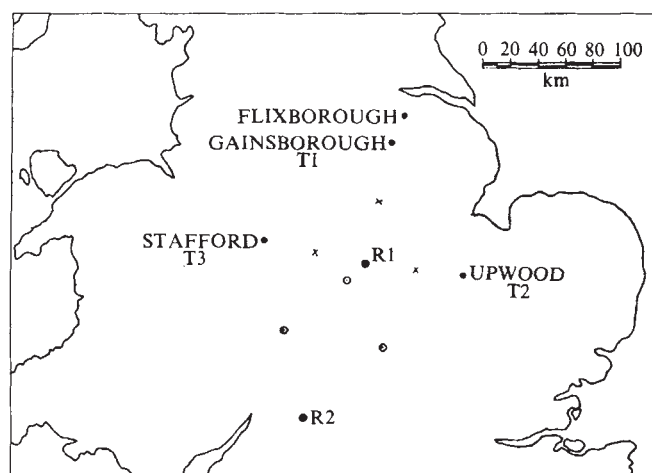


Fig. 1 Location of transmitters and receivers of the Doppler sounding system. T, Transmitter; x and o, propagation path mid points; R, receiver.

On June 1 three transmitters located at Gainsborough, Upwood and Stafford were operational. These were received at two sites, one at Leicester (R1) and one in Wiltshire (R2). Figure 1 shows the locations of the transmitters and receivers together with those of the six reflection points.

At 1600.20 GMT a major disturbance was noted on the Gainsborough-Leicester path and subsequently on the more

southerly transmissions. Recordings of frequency as a function of time were obtained from the two receivers R1 and R2 and the Leicester record is reproduced in Fig. 2. The frequencies of the three transmitters are offset by 3 Hz relative to each other so that they may be distinguished on the frequency-time recording. The principal feature on all six transmissions is the large quasisinusoidal oscillation starting at 1601.11 GMT on the transmission closest to the explosion (Gainsborough-Leicester). The feature approximates to two cycles of a sinusoidal oscillation with a period of about 50 s. The initial positive Doppler shift indicates that the electron-density

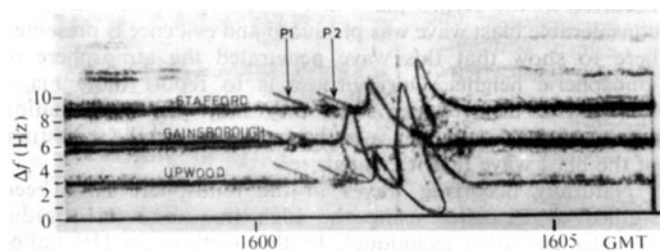


Fig. 2 Time variation of Doppler frequency shifts recorded by the Leicester receiver (R1) showing large-scale disturbances between 1600.20 and 1603.38 GMT.

is first enhanced, thus producing a lowering of the reflection level. This is followed by a negative Doppler shift indicating that the height increases rapidly. During the next half cycle the frequency shift is again positive showing a further period of decreasing height. Finally there is a very small negative Doppler shift as the height returns to its undisturbed position. The maximum Doppler frequency shift is 4.5 Hz which corresponds to a rate of change

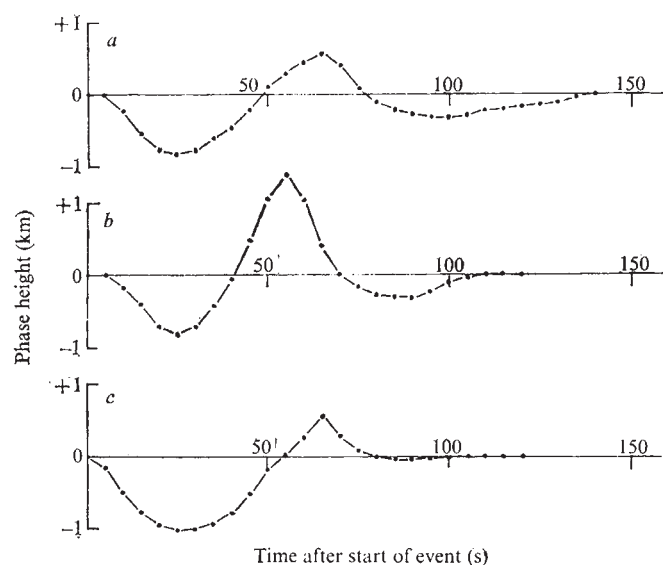


Fig. 3 Phase height changes produced by the disturbances, calculated from the Leicester observations. Time measured from the start of each disturbance. a, Stafford; b, Gainsborough; c, Upwood.

of 142 m s^{-1} in the reflection height. This frequency deviation is a factor of four greater than those produced by naturally occurring travelling disturbances in the ionosphere. An interesting feature of the Leicester recordings are the two precursors, marked P1 and P2 in Fig. 2, which precede the main event on all three transmissions. These features are less well defined

on the recordings obtained from R2.

The velocity c of an acoustic wave in the atmosphere is given by

$$c^2 = \gamma g H \quad (2)$$

where γ is the ratio of the specific heat of the gas at constant pressure to that at constant volume, g is the acceleration due to gravity, and H is the scale height of the atmosphere at the height considered. Using the CIRA reference atmosphere³ and equation 2, the time taken for an acoustic wave to travel from Flixborough to the reflection point of the Gainsborough transmission was found to be 10.6 min. The recording in Fig. 2 shows that the major disturbance started at 1601.11 GMT and so the time of the explosion is 1550.35 GMT. This is in fair agreement with the time of 1554 GMT reported in the national press. The presence of the two precursor events P1 and P2 is not yet understood but they clearly indicate that two distinct disturbances were produced in advance of the main event. This could result from two pressure waves separated by about 40 s at ionospheric heights.

The magnitudes of the disturbances recorded by R1 (Fig. 2) are greater than those obtained at R2. The increased amplitude of the disturbances probably results from the slightly greater reflection heights of the signals received at Leicester. The amplitude of the acoustic wave will increase exponentially with height, consequently the disturbance will be greater the higher the reflection point in the ionosphere.

The phase height change (h) produced by the passage of the disturbance has been determined by integrating the frequency-time recording since from equation 1

$$h = P/2 = - (c/f) \int \Delta f \cdot dt \quad (3)$$

The height changes for the various transmissions are shown in Fig. 3. The maximum displacement is about 1.5 km and the period of the wave is about 75 s. This corresponds to a quasi wavelength of 68 km assuming the velocity of sound to be 900 ms^{-1} at the reflection height.

A detailed analysis will be undertaken to determine the exact time of detonation and to estimate the magnitude of the pressure wave at its origin. The presence of the precursor events will be examined and the significance of the double feature investigated.

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The turbulent boundary layer on the continental shelf

IN the late summer of 1973 we made measurements of the current structure in the thermal boundary layer on the continental shelf. The measurements were taken under conditions of complete neutrality, well away from the influence of local

coastlines. Figure 1 shows the positions of two moorings, 001 ($48^{\circ} 10.5'N$, $07^{\circ} 54'W$), and 002 ($48^{\circ} 16.5'N$, $07^{\circ} 47'W$) separated by 15 km. This compares with a tidal excursion of about 10 km for the surface water. Both moorings were in 180 m of water and more than 200 km from the nearest mainland. The current meters were supported by subsurface buoyancy. The thermal structure of the water column, and the depths at which current meter observations were made in relation to the thermal boundary layer is shown in Fig. 2. The temperature of the bottom 100 m of the water column increases with depth. This marginal increase of temperature at the adiabatic rate ($1.3 \times 10^{-6}^{\circ}C\ cm^{-1}$) is expected of a turbulent boundary layer, because the production of turbulent energy is much greater than the stabilising effect of the buoyancy flux. The absolute accuracy is only $0.02^{\circ}C$, using a mercury-in-glass reversing thermometer as the calibration standard. The resolution is, however, considered quite genuine to $\pm 0.0005^{\circ}C$ (ref. 1).

All but one of the current meters gathered reliable current data during the same seven day period. The meter which was placed 30 m off the bottom, failed after only two days and is excluded from the analysis. For the short period that it was in operation, however, it was consistent with the measurements obtained at a slightly shallower depth, 33.5 m off the bottom. The data reduction was identical for all of the current meter records.

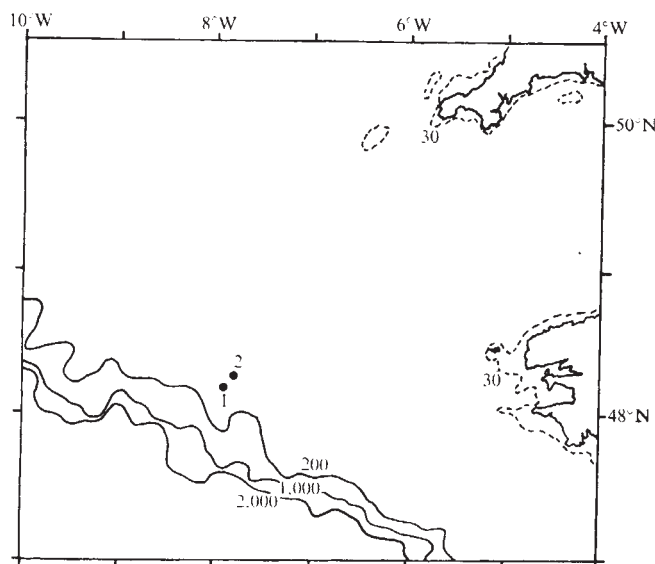


Fig. 1 Positions of moorings (●). Depth contours at 30 m, 200 m, 1,000 m and 2,000 m.

Kinetic energy density spectra for the current records were obtained from 2,048 two inch data points which were sampled every five minutes using a fast Fourier algorithm for complex numbers. Spectra for the current meter records obtained from mooring 001 are shown in Fig. 3. The kinetic energy density is generally less for the current meter records closest to the bottom but is evenly distributed throughout the frequency range except at the highest frequencies. The variance at the high frequencies is greatest on the record furthest from the bottom, which may be because of internal waves travelling along the thermocline. These results were also obtained for mooring 002.

Of the total kinetic energy, 80% is contained between the spectral estimates 11.4^{-1} and 13.2^{-1} cycles per hour, centred on 12.2^{-1} cycles per hour. This represents the bulk of the tidal stream energy. We have chosen this estimate to represent the motion because it represents about 90% of the mean speed.

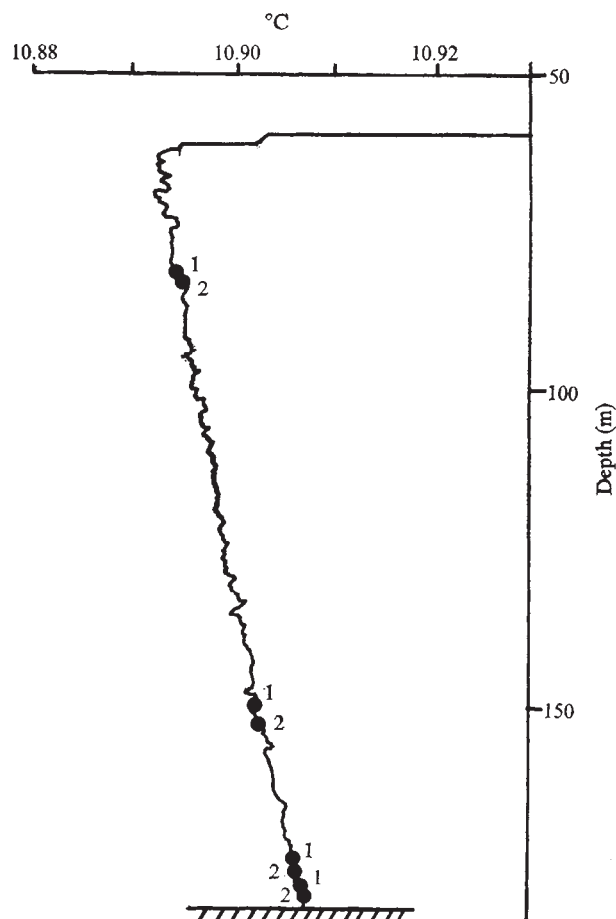


Fig. 2 Thermal structure of the water column in the turbulent boundary layer obtained from a typical temperature profile showing the depths at which current meters were fixed in this layer (●).

To avoid a time varying analysis the kinetic energy density spectra for each record was split into clockwise and anticlockwise spectral estimates. An example of this is shown for the bottom current meter record of mooring 001 (Fig. 3). The vector addition of clockwise and anticlockwise components produces a series of ellipses.

Table 1 summarises the results obtained for the semidiurnal estimate of all the records. At semidiurnal periods 94% of the kinetic energy is contained in the clockwise motion. Table 1 also shows the semimajor (a) and semiminor (b) axes of the tidal ellipse and the ratio $-b/a$. These show that the tidal ellipses are geometrically similar but become reduced in scale as the bottom is approached; a semimajor axis of $\sim 55\ cm\ s^{-1}$ 100 m from the bottom drops to $\sim 32\ cm\ s^{-1}$ 2 m from the bottom. The ellipses are orientated such that their major axes lie roughly parallel with a line drawn through the two mooring positions. A clear difference in orientation exists between the records from different moorings, with mooring 002 rotated about 8° clockwise with respect to mooring 001. The mean phase differences, which are relative to the lower current meter on mooring 001, are less than 3° apart in the bottom 33.5 m of the water column. That is approaching the limits of the absolute accuracy obtainable using different meters. The uppermost current meter on both mooring is, however, lagging about 13° (anticlockwise) behind the lower meters. Mooring 001 as a whole, lags behind mooring 002. That is confirmed by a simple overlay of direction records.

Figure 4 summarises the distribution of clockwise tidal amplitude [$u(-)$] with respect to depth (Z). The logarithmic depth (m) above the bottom is plotted against the clockwise semidiurnal speed ($cm\ s^{-1}$). This plot has been chosen to admit

Table 1 Current meter results

Water depth (m)	Mooring	Height of current meter above bottom (m)	Kinetic energy at semidiurnal frequency (%)	Semidiurnal energy in the clockwise component (%)	Relative phase of current ellipse (degrees)	Semi-major axis, <i>a</i> (cm s ⁻¹)	Semi-minor axis, <i>b</i> (cm s ⁻¹)	- <i>b/a</i>	Orientation of major axis (°T)
188	001	98.0	79	96	-013	51.6	-33.2	0.64	031
	001	33.5	80	93	-003	45.1	-25.3	0.56	027
	001	7.5	83	93	-002	38.8	-22.4	0.57	033
	001	3.5	82	94	000	35.2	-21.4	0.61	026
184	002	98.0	79	95	-007	58.0	-35.6	0.61	042
	002	5.0	80	92	+006	36.4	-20.2	0.56	035
	002	2.0	82	93	+006	32.1	-18.6	0.58	034

possible inferences with turbulent boundary layer theory.

In the plot of Fig. 4 the data fits the form

$$u(-)/u_*(-) = (1/k) \log_e Z/Z_0$$

where $k=0.4$, $u_*(-)=1.2 \text{ cm s}^{-1}$, and $Z_0=3 \times 10^{-4} \text{ m}$, for $Z < 33.5 \text{ m}$.

Such logarithmic plots can, however, be matched with power laws for selected ranges, and the data could have equally been put in the form

$$Z/Z_1 = (u/u_1)^n$$

where $n=8$, and at $Z_1=1 \text{ m}$, $u_1=24 \text{ cm s}^{-1}$.

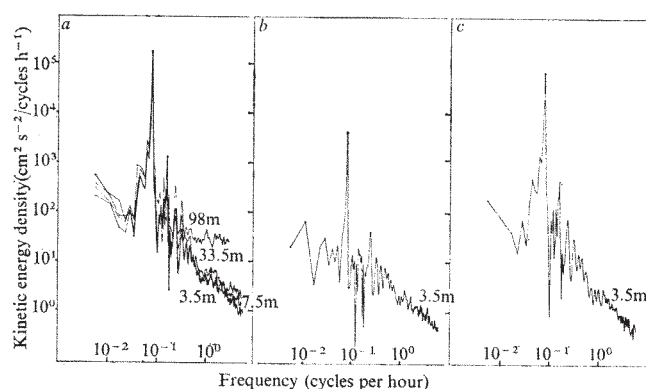


Fig. 3 Kinetic energy density spectra for records obtained on mooring 001. The total kinetic energy density has been split into anticlockwise and clockwise estimates for the current meter nearest the bottom: a, total density; b, anticlockwise; c, clockwise.

Identification of the logarithmic form with a boundary layer, where $u_*(-)$ represents the friction velocity and Z_0 the characteristic length scale relating to the boundary roughness, requires some independent confirmation. Such a form is strictly applicable only to an unaccelerated, one-dimensional flow under negligibly small pressure gradient. In a tidal stream, however, the flow is accelerated and pressure gradient forces, geostrophic forces and centrifugal forces are important. Applicability of the logarithmic form in the unsampled lower two metres may be extended through measurements in the coastal waters of Red Wharf Bay, although we have no values of current direction here². The homogeneous nature of the temperature in the bottom mixed layer suggests that eddy viscosity is related to distance from the boundary.

Two lines have been drawn in Fig. 4 as the values come from different moorings and both suggest that the flow is hydrodynamically rough (the bottom surface is sand and broken and abraded shells). The uppermost records clearly do not fit this logarithmic form and they are undoubtedly influenced by the thermocline and the boundary at the sea surface. Temperature measurements made from the upper two metres showed that the thermocline descended semi-diurnally below the uppermost current meter. This effect was

mainly responsible for the phase lag of the uppermost meter on each mooring. Continuous temperature records obtained from the other current meters showed no vertical temperature differences within instrumental resolution (0.03° C) during the complete seven day period, and this confirms the view that Fig. 2 represents a very persistent state of neutrality within 30 m of the bottom on the continental shelf.

The friction velocity of the anticlockwise component, $u_*(+)$ can be determined from Table 1, which shows that the anticlockwise energy is only $\sim 7\%$ of the semidiurnal energy on the records below 33.5 m. This gives $u_*(+)=0.3 \text{ cm s}^{-1}$. The time varying friction velocity is found by adding:

$$u_*(t) = u_*(-) \exp(-i\omega t) + u_*(+) \exp(i\omega t)$$

where ω is the angular velocity (rad s^{-1}) of the semidiurnal

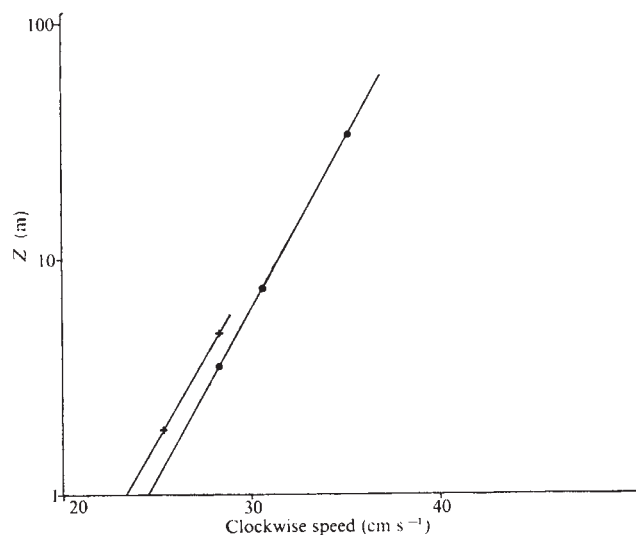


Fig. 4 The logarithmic profile for the clockwise semidiurnal motion.

tide. The friction velocity then varies between $0.9\text{--}1.5 \text{ cm s}^{-1}$. Our observations extend from spring to neap tides and so the values of $u_*(t)$ and Z_0 describe an approximate mean situation for the turbulent boundary layer of the continental shelf.

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Empirical relationship for the critical temperature of some A15 superconductors

A NEW, empirical relationship¹, which links the T_c of A15 superconductors—based on the A_3B stoichiometric ratio—with the atomic mass, M_B , of the B element, indicated that $\log T_c$ is a linear function of $\log M_B$ and that high T_c values can be predicted if M_B is small. A B element is from group IVB (Si, Ge and Sn) and an A element is from group VA (V, Nb and Ta).

The subsequent discovery that stoichiometric Nb_3Ge has the highest known T_c —23.2 K (ref. 2)—provides an opportunity to test further the $\log T_c$: $\log M_B$ relationship. The original prediction for Nb_3Ge was 29–30 K (ref. 1). If the experimental value, 23.2 K, is accepted as correct then the $\log T_c$: $\log M_B$ plot, using the additional data in Table 1, defines for the Nb and Ta series, two accurately parallel lines, with a slope of $-\frac{1}{2}$.

Table 1 Transition temperatures (experimental) of some A15 compounds

	V*	Nb*	Ta*
Si†	17.1(4)‡	Not known	Not known
Ge†	7 (3)	23.2(2)	8 (16)
Sn†	4.3(3)	18.3(17)	6.4(18)

* A elements.

† B elements.

‡ Reference numbers are in brackets.

The deviation of the V alloys from this sequence occurs because some of the T_c data refer not to the stoichiometric A_3B ratio (without which accurate comparisons between systems cannot be made) but to non-stoichiometric compounds with a V content greater than 75 atm. % (ref. 3). Thus, although V_3Si is well characterised at 17.1 K for stoichiometric single phase ordered samples (refs 4 and 5, and B. A. Hatt, unpublished) the compositions of the equilibrium A15 phases in V-Ge and V-Sn are $V_{77}Ge_{23}$ (ref. 3) and about $V_{80}Sn_{20}$ (refs 3 and 6), respectively. In both cases additional experimental work would be needed on the metastable, stoichiometric A15 compounds to establish their T_c values, which would

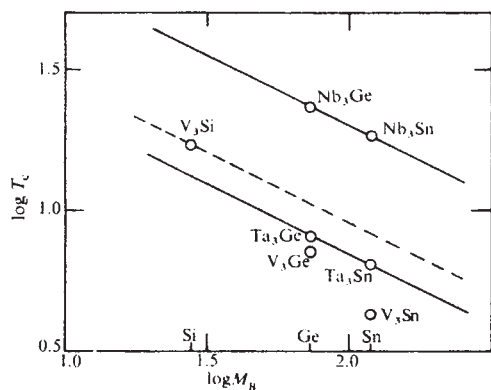


Fig. 1 $\log T_c$ against $\log M_B$ for binary A15 compounds of group VA and group IVB elements, where T_c is the superconducting critical temperature, and M_B is the atomic mass of the IVB element. Lines of slope of $-\frac{1}{2}$ are drawn through the points for the Nb and Ta compounds. The dotted line is drawn with a slope of $-\frac{1}{2}$ through the point for V_3Si .

certainly be higher than those quoted in Table 1. At present it must suffice to use the single point for V_3Si in order to define a dashed line, with a slope of $-\frac{1}{2}$, (Fig. 1), from which the predicted T_c values for V_3Ge and V_3Sn are 10.3 K and 8.3 K, respectively. These are reasonable estimates in the light of what is known of the effect of non-stoichiometry in other systems such

as V_3Si and V_3Ga (refs 4 and 7), and the extrapolation of data³ on V_3Ga – V_3Ge pseudobinary alloys yields a T_c of 10 K for stoichiometric V_3Ge .

Accepting the data used in Fig. 1 it emerges that T_c can be expressed as a function of $M_B^{-1/2}$ and that when presented in

Table 2 Slope, C , of lines in Fig. 2

C (K $u^{1/2}$)	Group VA element
90	V
198	Nb
69	Ta

this way (Fig. 2) the experimental plots for the Nb and Ta series extrapolate accurately to zero.

From Fig. 2 the transition temperature is expressed in the form $T_c = C/M_B^{1/2}$. The slope, C , for the three curves is given in Table 2. The relationship does not apply when the B element in A_3B comes from Group IIIB or the transition metals. It remains true, however, that when selected systems are compared, the Nb compound always has the higher T_c (for example, Nb_3Ga —20.3 K, and V_3Ga —15 K; Nb_3Al —18.9 K, and V_3Al —~9 K; Nb_3Au —11 K, and V_3Au —3.5 K).

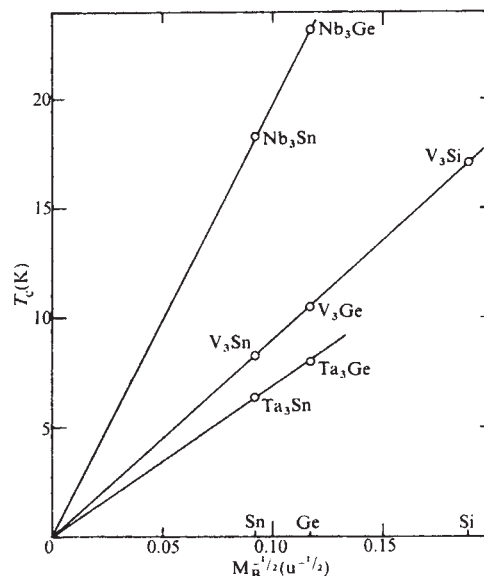


Fig. 2 T_c against $M_B^{-1/2}$ for the compounds shown in Fig. 1. T_c values for V_3Ge and V_3Sn are those estimated for the stoichiometric compounds from the dotted line in Fig. 1.

It is interesting to try to relate the values of C to those of some property of V, Nb and Ta (Table 3). The only property which varies in the same relative order as C , is the critical temperature, T_c (Table 3). C for the compound series has been plotted against T_c for the corresponding element (Fig. 3). A straight line can be drawn through the points. From Figs 2 and 3 it seems that, for an A15 compound A_3B , where A is either V, Nb, or Ta, and B is one of the group IVB elements Si, Ge and Sn, the superconducting critical temperature is given by:

$$T_c = 27.5 (T_A - 2) M_B^{-1/2}$$

where T_A is the critical temperature of pure A and M_B is the atomic mass of element B.

The existence of this empirical relationship raises three questions: first, what is its physical significance; second, why does it hold only for group IV elements; third, how far can it be used to predict higher critical temperatures?

The theory of Bardeen, Cooper and Schrieffer (BCS) gives

Table 3 Properties of elemented V, Nb, Ta to be compared with C (Table 2)

	$\theta_D(K)$	$T_c(K)$	$\gamma(mJ\ mol^{-1}\ K^{-2})$	$V_{ph}(10^{-2.3}\ eV\ cm^3)$	$T_m(^{\circ}C)$	$K(10^{10}\ N\ m^{-2})$	$Y(10^{10}\ N\ m^{-2})$
V	320-400	5.3	9.04	0.18	1920	15.80	12.76
Nb	240-280	9.2	7.66	0.34	2468	17.03	10.49
Ta	250	4.5	5.84	0.36	3010	19.63	18.57

* θ_D , Debye temperature; T_c , superconducting critical temperature; γ , electronic specific heat coefficient; V_{ph} , electron-phonon interaction parameter (data from ref. 8); T_m , melting point; K , bulk modulus (compressibility); Y , Young's modulus (data from ref. 9).

the critical temperature of a superconductor as

$$T_c = (1.14h/k) \langle \omega \rangle \exp(-1/N(o) V)$$

If it can be assumed that $N(o) V$ does not vary much among the compounds under discussion, the isotope effect must derive from the average phonon frequency, $\langle \omega \rangle$. In a monatomic crystal, the phonon dispersion relationship involves (isotope mass) $^{-1/2}$ and gives rise to the classical isotope effect in some pure metal superconductors. In a polyatomic crystal the dispersion relationship has more than one branch, each of which depends upon some average of isotopic masses, usually of the form $(\sum_i 1/M_i)^{1/2}$. At the zone boundary, however, the relationship for each branch reduces to a form which involves only one of the masses, that is $\omega \propto (1/M)^{1/2}$. Thus, the quoted empirical formula for T_c is rationalised if it can be assumed that the phonon modes involved in the BCS interaction are those close to the zone boundary. This has interesting implications

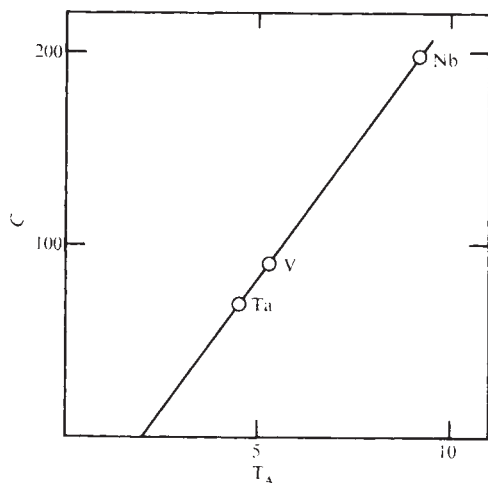


Fig. 3 The slope C , of the lines in Fig. 2, against T_A , the critical temperature of the group VA elements.

for the theory of superconductivity in these compounds. The fact that the important modes are those relating to the B atoms may also explain why, in the ternary compound $Nb_3(AIGe)$, an ordering of the A1 and Ge atoms is thought to be necessary to achieve maximum T_c (refs 10 and 11); disorder on the B-atom sites possibly disturbing these modes.

The similarity between elements in group IVB, both chemically and physically, is marked most strongly. They all have the same low temperature equilibrium crystal structure, and electrically are all semiconductors. This is not true of the group IIIB elements, and probably explains why a simple T_c relationship exists for compounds with IVB elements, but not for compounds with IIIB elements in which $N(o) V$ may no longer be a constant. The situation is more complicated when the second element is a transition metal, and the value of T_c depends on the position of the transition metal's d band relative to the Fermi level of the compound³.

Extrapolation of the Nb line in Fig. 2 suggests that if Nb_3Si crystallises in the A15 structure, it should have $T_c \approx 38\ K$, which would make it by far the highest T_c superconductor, with distinct economical advantages. It does not exist in equilibrium because the silicon atom radius is too small; the ratio of the radii of the two component atoms must lie between 0.85 and 1.15 in order for a stable A15 structure to form¹². An ordered (Cu_3Au) structure for this composition, with $T_c = 1.5\ K$, has been reported¹³. Codeposition of the evaporated elements onto a heated substrate has produced a non-stoichiometric A15 phase, with a maximum T_c of 9.3 K at a composition of 21 atom % Si (ref. 14). More recent attempts to form Nb_3Si under high pressures have been unsuccessful¹⁵. It may be possible to get some enhancement of T_c in a ternary compound $Nb_3(GeSi)$. The Ge-Si ratio should be such as to permit ordering on their sub-lattice, but the fraction of silicon atoms should not be so large that a weighted average radius differs by much more than 15% from the radius of the Nb atom. The compound $Nb_3(Ge_{0.75}Si_{0.25})$ fulfils these conditions, and if a weighted average of the Ge and Si atomic masses is appropriate, and if it forms a stable A15 compound, it should have a critical temperature of 25.2 K.

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An interfacial isotope effect

RADIOACTIVE carbon is utilised commonly to tag compounds used in interfacial studies. As is usual in studies with isotopes of carbon, it has been assumed tacitly that the radioactive surfactant behaves exactly like the untagged or inactive compound. During a study¹ of condensed monolayers at the water-air interface, however, a significant kinetic isotope effect was observed in their stability behaviour.

Stearic-1-¹⁴C acid (Dhom Products), which has a specific activity of 58 mCi mmol⁻¹, was mixed with inactive stearic acid to yield a 14.3 mCi mmol⁻¹ mixture with 23.1% ¹⁴C-labelled carboxyl groups. This particular stearic-1-¹⁴C acid sample was selected because, in addition to its purity (99.5% C₁₈, 0.2% C₂₀, and 0.3% C₂₂ saturated acids), its surface pressure-area isotherm (Fig. 1) is almost identical

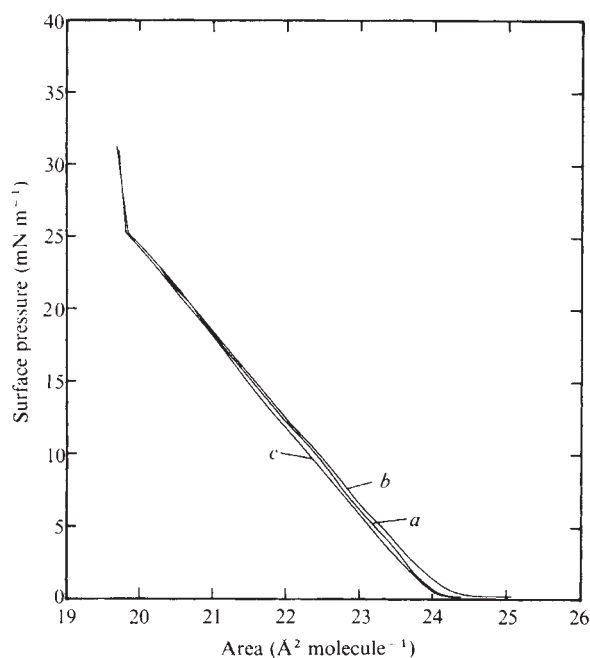


Fig. 1 The surface pressure-area isotherms of stearic acid monolayers on pH 2.00 subsolutions (corrected to have the same area at 30 mN m⁻¹ as inactive stearic acid). *a*, Inactive stearic acid; *b*, stearic-1-¹⁴C acid; ¹⁴C-labelled stearic acid. Compression rate=1.5 Å² molecule⁻¹ min⁻¹; temperature, 20.7° C.

to that of the highly purified inactive stearic acid (99.6% C₁₈, 0.2% C₁₆, and 0.2% C₂₂). Stearic acid was deposited from purified hexane spreading solutions on to either calcium free or 10⁻⁴ M CaCl₂ (ultrapure) subsolutions prepared from triply distilled water to which HCl, KHCO₃, or 10⁻³ M KHCO₃ and KOH of AR quality were added to vary the pH of the subsolution. The monolayers were compressed to a surface pressure of 31 mN m⁻¹ with an automatically recording Langmuir-type film balance designed for constant pressure operation. An indication of the monolayer stability was obtained by determining the decrease in the film area as a function of time, at constant surface pressure.

The measurements of monolayer stability in surface films of condensed stearic acid at pH 2.0 and 6.0, are shown in Fig. 2. The stability measurements of Ca-H-St monolayers (stearic acid monolayers on subsolutions containing calcium) were compared at intervals of 15 min and plotted (Fig. 3) as a function of the pH of the subsolution. The large decrease in the film area of inactive unionised

stearic acid films (Figs 2 and 3) result from a slow process of monolayer collapse in which crystals of stearic acid form slowly at the water-air interface. (The stearic acid and Ca-H-St monolayers consist principally of unionised stearic acid molecules below subsolution pH values of 5.5 and 4.2, respectively. The slow collapse of the monolayer is different from the catastrophic collapse observed by a number of other investigators.) Figure 2 also shows that the ¹⁴C-labelled stearic acid monolayer is more stable than the corresponding inactive monolayer. This result is not expected because the isotopic substitution occurs at an atom which is not immediately involved in the bonds that break and form as the fatty acid molecules transfer from the monolayer state to the collapsed bulk phase. This significant difference in the behaviour of the monolayer stability is attributed to a secondary kinetic isotope effect. The rate of change of the film area decrease and the isotope effect (¹²C/¹⁴C) both become greater with increasing time of compression. Figure 3 also shows that there is a difference in the stability behaviour between inactive monolayers and ¹⁴C-labelled Ca-H-St monolayers. At pH < 5.0, where the molecules are dominantly unionised stearic acid, the radioactive Ca-H-St monolayer is more stable; both monolayers possess the same stability in the pH range 5.0-7.8; and then above pH 7.8 a reversal in stability occurs with the inactive Ca-H-St monolayer becoming much more stable.

Several considerations indicate strongly that the observed stability differences do not arise from impurities in the

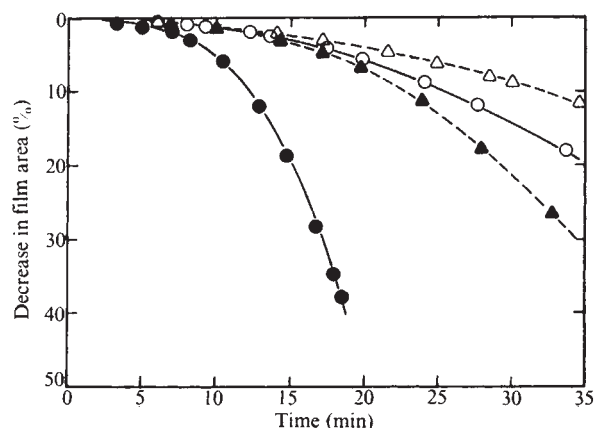


Fig. 2 Stability measurements of stearic acid monolayers at 31 mN m⁻¹. ○●, pH=2.0; △▲, pH=6.0; ●▲, inactive; ○△, ¹⁴C-labelled. Temperature, 20.5° C.

system. The high purity of the stearic acid samples minimises the effect of chemical impurities; and impurities arising from radiolysis would be expected to decrease the stability of the Ca-H-St monolayer throughout the pH range, not just on alkaline subsolutions. Furthermore, the peculiar stability behaviour of the ¹⁴C-labelled Ca-H-St monolayer, which rises to a maximum and then decreases again with increasing alkalinity, and the magnitude of the stability differences seem to rule out the impurity explanation.

The stability increase of ¹⁴C-labelled unionised stearic acid monolayers arises apparently from increased intermolecular forces of attraction between the carboxyl head groups and/or between the carboxyl groups and the water molecules of the subsolution. An increase in the carboxyl-group interactions is not, however, the sole effect of the isotopic substitution, because the stability of ¹⁴C-labelled Ca-H-St monolayers on alkaline subsolutions is not in-

creased similarly. Isotopic substitution of ^{14}C shifts the $\text{C}=\text{O}$ stretching fundamental from 1,715 to 1,637 cm^{-1} because of the difference in isotopic mass². The zero-point energy of the $^{14}\text{C}=\text{O}$ bond is thus lower than that of the $^{12}\text{C}=\text{O}$ bond, and the dipole moments of the two isotopic modifications of the $\text{C}=\text{O}$ bond will be slightly different because of vibrational anharmonicity. Because the dipole moment increases in deuterium substituted molecules³, it is assumed that ^{14}C -isotopic substitution also increases the dipole moment. Consequently, there should be an increase in the hydrogen-bond energy between the carbonyl oxygen atoms of the head groups and the hydrogen atoms of the water molecules and, as observed, an increase in the stability of the monolayer. The stabilising influence of the carboxyl ^{14}C atom seems to have its origin in the hydrogen bonding or dipole-dipole interactions between the carboxyl head groups and the subsolution water molecules.

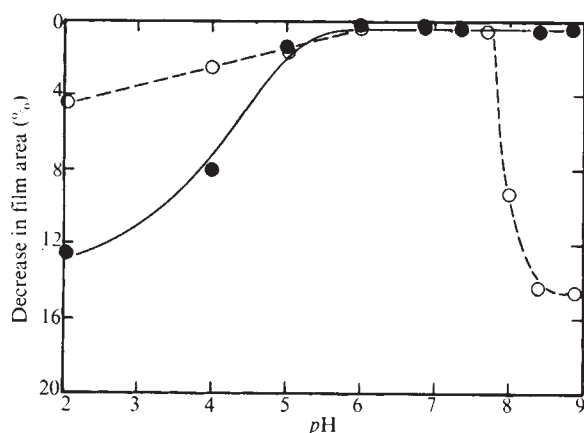


Fig. 3 Comparison of the stabilities of Ca-H-St monolayers at 31 mN m^{-1} , with compression time of 15 min at a temperature of 20.6° C. ●, inactive; ○, active.

The sudden decrease in the stability of ^{14}C -labelled Ca-H-St monolayers above pH 7.8 corresponds to a significant increase in the rate of monolayer collapse¹. Apparently the isotopic substitution affects the charge distribution within the calcium stearate surface micelles so that the molecular interactions between the coordination complexes and the subsolution water molecules are weaker than they are in the presence of untagged carbon atoms (R. D. Neuman, unpublished).

It is conceivable that compounds with a high specific activity, which exist in the highly oriented arrays of the two-dimensional state, may exhibit effects not observed commonly in bulk systems. The observed kinetic isotope effect indicates that the presence of tagged atoms in the head groups of surface active agents may significantly influence interfacial phenomena. Unfortunately, this interfacial isotope effect is not understood completely and needs further clarification.

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Geographic and temporal development of plagues

ALTHOUGH deterministic and stochastic descriptions of localised epidemics abound in the literature of epidemiology and quantitative biology^{1,2}, the geographic spread of epidemics has not been analyzed in such detail. (Although in ref. 2, page 205, Bailey gives equations similar in spirit to my equation (1) they seem to lack physical significance.) Realistic mathematical models of the geotemporal development of plagues could be useful in the study of epizootics (that is, in ecology, wildlife management or veterinary medicine), of social phenomena (such as the spread of drug abuse or fads), and of history. Needless to say, such models should also be applicable to public health questions.

I report here the results of an investigation of the propagation of epidemics using a simple, but plausible, deterministic model, and compare them with Langer's data on the Black Death of 1347-50 (ref. 3). First I describe the model, then explore its mathematical properties and in particular its ability to sustain wave-like (propagating pulse) solutions, compare its predictions with existing data³, and finally discuss its shortcomings and suggest directions for further research.

To describe the progress of plagues as simply as possible, it is convenient to assume only two interacting populations which can be taken to be infectives and susceptibles, although one might equally well consider hosts and parasites (for example, rats and fleas) or humans and vectors. We can express the change with time of the number of infectives within a small area as the rate of transitions from the susceptible population, less the removal rate (defined as the mortality, plus recovery, plus the net physical outflow from the area). The temporal variation of the susceptible population can be expressed similarly, except that the transitions from susceptible to infective appear as a net loss, and that the rate of removal is merely the net outflow. It is reasonable to suppose that, under the conditions obtaining during plagues, the net outflows of the infective and susceptible populations result from random walks rather than mass migrations, and thus can be represented as simple diffusion. The resulting equations are:

$$\frac{\partial I}{\partial t} = KIS - \mu I + D \left(\frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} \right) I \quad (1a)$$

$$\frac{\partial S}{\partial t} = -KIS + D \left(\frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} \right) S \quad (1b)$$

where S and I are the susceptible and infective population densities, μ is the mortality rate (which for simplicity I have represented as a Poisson-distributed process) and the transition rate from I to S is proportional to the rate of binary encounters between infectives and susceptibles. The transmissibility coefficient K may be expressed in terms of more fundamental quantities:

$$K = 2 \int_0^\infty db b \int_0^\infty dv v \Phi(b, v) f(b, v) = 2 \langle b v f \rangle \quad (2)$$

where $f(b, v)$ is the infection probability as a function of distance of encounter, b , and velocity v , and $\Phi(b, v)$ is the distribution function for encounters. This K represents the average area of infection swept out by an infective per unit time, and KS is therefore the number of new infectives produced per unit time, per infective. The diffusion constant, D is assumed the same for both groups, since there is no good reason to assume it is not the same. The model represented by equations (1) and (2) is usually described as deterministic although it incorporates probabilistic ideas in three places (the rate of binary encounters, the random walks leading to a diffusion term, and the Poisson-distributed mortality) because it admits of numerically precise solutions and gives no idea of what the variance of I and S should be. (Although we should clearly expect the variances of the numbers of individuals to be found in the area dA to be roughly $I dA$ and $S dA$, respectively, by analogy with other counting experiments.)

Since we are interested primarily in the simple case in which the initial susceptible population density is uniform, $S(\vec{x}, 0) = U$, we can reduce equation (1) to dimensionless form by scaling:

$$\begin{aligned} I &\rightarrow UI \\ S &\rightarrow U/S \\ x &\rightarrow (D/KU)^{1/2} x \\ t &\rightarrow (KU)^{-1} t \end{aligned}$$

and so

$$\frac{\partial I}{\partial t} = IS - \lambda I + \left(\frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} \right) I \quad (3a)$$

$$\frac{\partial S}{\partial t} = -IS + \left(\frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} \right) S \quad (3b)$$

where $\lambda = \mu/KU$.

Langer's map, in which contours of the progress of the black death are drawn for equally spaced time intervals (Fig. 1), strongly suggests wave-like propagation of this disease. For this reason I have investigated whether equation (3) can support propagating one-dimensional (plane) waves. Letting $I(\vec{x}, t) = I(x - vt)$ and $S(\vec{x}, t) = S(x - vt)$, we obtain the coupled, second-order ordinary differential equations

$$-vI' = IS - \lambda I + I'' \quad (4a)$$

$$-vS' = -IS + S'' \quad (4b)$$

These equations constitute a nonlinear eigenvalue problem. The interesting question is, for what values of λ will the equations have solutions satisfying the conditions

$$\begin{aligned} I(-\infty) &= I(\infty) = 0 \\ 0 \leq S(-\infty) &< S(\infty) = 1 \\ I, S, v &> 0? \end{aligned}$$

Adding equations (4a) and (4b), we find

$$\frac{d}{dx} [I(x) + S(x)] = \lambda e^{-vx} \int_{-\infty}^x e^{vx'} I(x') dx' > 0 \quad (5)$$

so that

$$I(x) + S(x) < I(\infty) + S(\infty) = 1 \quad (6)$$

On the other hand, if we integrate (4b) from $-\infty$ to $+\infty$ we obtain (note $S'(-\infty) = S'(\infty) = 0$)

$$\Delta S = S(\infty) - S(-\infty) = \frac{1}{v} \int_{-\infty}^{\infty} dx I(x) S(x) \quad (7)$$

However, integrating (4a) from $-\infty$ to $+\infty$ we find

$$\lambda \int_{-\infty}^{\infty} dx I(x) = \int_{-\infty}^{\infty} dx I(x) S(x) = v \Delta S \quad (8)$$

and since $0 < S(x) < 1$ for all x ,

$$\int_{-\infty}^{\infty} dx I(x) > \int_{-\infty}^{\infty} dx I(x) S(x) \quad (9)$$

or

$$\frac{v}{\lambda} \Delta S > v \Delta S$$

That is, wave-like solutions can only exist if

$$\lambda = \mu/KU < 1 \quad (10)$$

This criterion which the ratio of the rate constants, μ and KU , must satisfy has an obvious physical interpretation: if the infectives die too rapidly, they cannot spread the disease; whereas if the population density multiplied by the transmissibility factor K is too small, the plague cannot be transmitted either. (I should add that it is straightforward to show that outward-propagating circular waves are also solutions of equations (3); see also ref. 2, page 205.)

There are various ways one might attempt to find an approximate solution of equations (4) and thereby estimate v as a function of λ . I thought it more interesting to consider the original partial differential equation in order to see explicitly how wave-like solutions arise. I have therefore solved numerically the (one-dimensional) equations

$$\frac{\partial I}{\partial t} = IS - \lambda I + \frac{\partial^2 I}{\partial x^2} \quad (11a)$$

$$\frac{\partial S}{\partial t} = -IS + \frac{\partial^2 S}{\partial x^2} \quad (11b)$$

on a spatial mesh of 100 points. The development of and final form of the propagating solutions is essentially independent of the initial distributions $I(x, 0)$ and $S(x, 0)$, as long as they bear some resemblance to a plague locus entering a previously uninfected population of susceptibles. (When the ratio μ/KU exceeds the critical value, unity, initial perturbations rapidly die away.) A typical propagating solution is shown in Fig. 2. The (approximate) velocities of propagation, the maximum density of infectives, and surviving populations are given in Table 1 for various values of μ/KU .

At the time of the Black Death (1347 AD) the population density U of Europe was about 50 mile⁻². To try to get a rough idea of what D should be, we note that communication was such that one might expect minor news or gossip to diffuse a distance on the order of 100 miles in a year, that is $D \sim 10^4$ mile² yr⁻¹ (ref. 4). The area swept out in ambulation at a nominal 1 mile h⁻¹ slow walk, assuming $\langle fb \rangle \sim 0.5$ foot (corresponding to a 5-foot flea-hop times a 10% average transmission probability) is 0.4 mile² yr⁻¹ and so $KU \sim 20$ yr⁻¹. Assuming a mortality rate of $\mu \sim 15$ yr⁻¹ (corresponding to a 2-week infectious period) we expect a velocity of propagation of 200–400 mile yr⁻¹. This velocity is in substantial agreement with that which can be estimated from Fig. 1. (All the numbers given above were educated guesses, but the resulting speed is insensitive to their values since $v \sim \sqrt{KUD}$. My object in making these guesses was primarily to indicate the reasonableness of the model and its predictions.)

The results reported here can be summarised as follows. The gross features of the geographical progress of epidemics can be described by means of a deterministic model which is strongly reminiscent of models which have been used to describe chemotaxis⁵, propagation of neural impulses⁶, complex organic chemical reactions^{7,8}, and the advance of advantageous genes along a one or two-dimensional habitat^{9–11}. The model presented here gives rise to propagating solutions whose velocities are (primarily for dimensional reasons) comparable with the observed velocity of the Black Death of 1347 AD when the physical constants in the model are set to reasonable values. It is particularly important that, given the infectious period of the disease (essentially the time for removal of a diseased individual from the population of infectives) and its transmissibility, K , we can estimate the



Fig. 1 Approximate chronology of the black death, 1347 to 1350 (From *The Black Death* by William L. Langer. Copyright © 1964 by Scientific American, Inc. All rights reserved.)

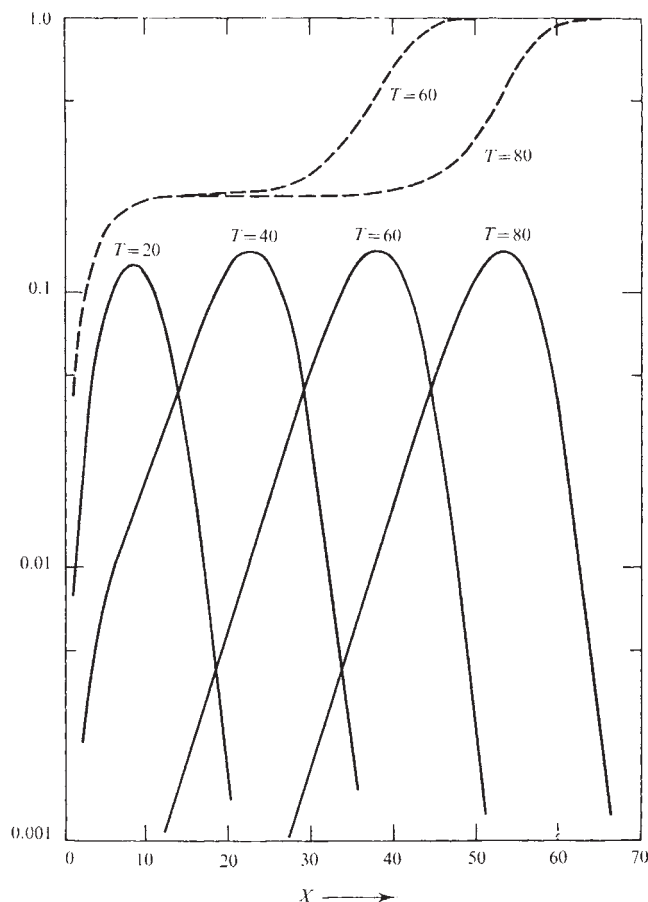


Fig. 2 A typical numerical solution of the (one-dimensional) equations (11a) and (11b) which shows clearly the pulse-like character of the plague after the introduction of the initial infection. The equations were solved on the spatial interval $0 < x < 100$ in unit steps and with time-steps of 0.5. The distributions of susceptibles, $S(x, t)$, are indicated by dashed lines after 60 and 80 time steps. The distributions of infectives after 20, 40, 60, and 80 time steps are indicated by the solid lines. The initial distribution of susceptibles was uniform and equal to unity, whereas that of the infectives was zero for $x > 5$, and consisted of 5 random numbers lying between 0 and 0.01, for $1 < x < 5$. Repeated runs indicate that after 20 time steps the distributions are independent of the initial ones, for a very wide range of initial infectives introduced in the vicinity of $x=0$. (Note also that the precipitous drop in $S(x, t)$ near $x=0$ is an artefact of the boundary conditions, which remains fixed in space and which does not reflect the true number of remaining susceptibles after the plague wave has passed.) $\lambda=0.5$.

critical (minimum) population density necessary for the outbreak of epidemics:

$$U > U_{crit} = \mu/K. \quad (12)$$

This relation may have some use as a historical tool, since if K and μ are known for a given type of epidemic, and if D can be estimated more accurately than was possible herein, for a given terrain and cultural level, then the local value of U can be extracted from the observed advance of plague fronts. Moreover, if we consider the maximum value of I in the wave, we see that it decreases monotonically with λ , and so gives an independent estimate of μ/KU . Finally, if we apply a reasonable model of the inheritance of susceptibility to estimate the relative frequency of susceptibles and immunes after a given period of time, starting from some initial relative frequency, and if we take into account the recurrence time for major historical epidemics of a given kind, we should be able to at least check for self consistency estimates of population and of plague severity such as those quoted by Langer³.

It is also interesting to extract from the solutions of this model the appearance of the plague wave to a stationary observer. He would see an extremely sudden onset of the

disease, during which some fraction of the susceptibles catch the disease, followed by the afflicted dying. Note that in these calculations, not all of the susceptibles become infected and die. The survivors of high-mortality plagues $\mu/KU > 0.5$ are therefore a mixture of the immune and the merely fortunate. Paradoxically, the more rapidly fatal the disease is on an individual basis, the better it is for the population. (This is, of course, well known from the theory of localised epidemics.) Because of the existence of a critical value, μ/K , of the susceptible density, we expect the actual development of a plague to follow the sequence: (1) increase of U by general population growth or in-migration past U_{crit} and thereby the creation of a substantial instability toward a plague wave; (2) introduction of the plague agent above the minimum threshold; (3) extremely rapid development of plague. The present situation of many industrialised nations is such that the density of susceptible individuals is at least a factor of 10 greater than that which obtained in mediaeval Europe. The present calculations suggest that any serious outbreak of bubonic plague, such as might be expected to follow a lengthy disruption of medical services, would result in the death of essentially all the susceptibles. What fraction of the population might be so described is not clear, especially in the face of possible mutations of the responsible microorganisms, but it probably is at least 25% and might exceed 75%.

Table 1 Parameters of plague waves for several values of the damping parameter $\lambda = \mu/KU$

μ/KU	v (in units of $\sqrt{KUD}$)	I (max)	S_i
0.10	2.0	0.7	~ 0
0.25	1.9	0.4	~ 0.025
0.50	1.5	0.14	0.22
0.75	0.8	0.03	0.6
0.90	0.55	0.004	0.8

There are several grounds on which to criticise the present model. First, the usual density distribution of human populations is clumped, not uniform (because people tend to live in villages and cities); and second, the model takes only the most elementary account of chance. As long as we do not attempt too detailed a simulation, averaging over the clumps will doubtless give the same gross predictions as the uniform distribution. On the other hand, the major divergence of the results of the deterministic model from those of the more fundamental stochastic approach is most likely to be that the latter would also predict a minimum threshold for the number of initial cases of the disease, below which propagating solutions are improbable. (We would expect this effect because statistical fluctuations would tend to damp out a small outbreak with near certainty.)

It is worth reiterating that models such as that presented here could be applied directly to the study of epizootics and should therefore be useful in ecology, wildlife management and veterinary medicine. Further, the spread of certain mass sociopsychological phenomena (such as new religions) might be sufficiently similar to that of plagues as to be worth investigating by similar methods.

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Identification and follow-up of infants at risk of sudden death in infancy

In the past 10 yr infant deaths in the age group 1 week up to 1 yr have levelled off at about 7.5 per thousand. About half these deaths are sudden and unexpected and are consequently referred to a coroner for certification; subsequent *post mortem* investigation reveals evidence of disease likely to cause death in 30% of sudden deaths: in the remainder the cause of death is obscure and such a case may be described as sudden infant death syndrome, SIDS, or more conveniently as cot death. In 1972 a panel, convened by the National Institute of Child Health and Human Development, Washington, to discuss the status of epidemiological research in SIDS considered a prospective study of high risk babies of primary importance, but doubt was expressed as to whether a sufficiently high risk group could be identified to make such a study feasible (P. Froggatt, personal communication). We report the results of the first year of such a prospective study.

To determine means of identifying high risk babies at or soon after birth, detailed obstetric and perinatal histories were abstracted for 119 cases of sudden infant death and 135 live controls born in the same hospitals¹. In this study we excluded cases of sudden infant death associated with serious congenital anomaly, for example, congenital heart defect or Down's syndrome. We intended that the high risk group should include both explained and unexplained deaths. The former group, comprising 29% of the 119 cases, are potentially preventable and their identifying characteristics were found to differ little from those of the unexplained deaths.

From univariate tabulations a set of 40 variables were selected which could be ascertained at or soon after birth and which gave some indication of being of prognostic value. Stepwise discriminant analysis showed that the variables, shown in Table 1 in order of importance, were statistically significant. The sign of the coefficient indicates whether estimated risk increases as the variable increases. For example, the risk decreases as the age of the mother increases and also if her blood group is A and if she intends to breast feed the baby. Conversely, the risk increases as the birth order of the child increases and if the blood group is O, B or AB. Using these variables Mahalanobis' generalised squared distance between the groups is 1.62 and the observed

Table 2 Number of infants, sudden deaths and hospital admissions in various groups of the prospective study

Group	No. in group	No. deaths	Risk relative to B	Hospital admissions	
				No.	% of group
B	5,077	7	1.0	180	3.5
A not selected	477	4	6.1*	42	8.9
A followed up	354	—	—	25	7.1
A did not participate	80	1	9.1†	9	11.3
Excluded congenital anomaly	15	—	—	—	—

* $0.005 > P > 0.001$. † $0.05 > P > 0.01$.

discriminant scores were approximately normally distributed. This implied that a high risk group comprising 15% of the population with the highest scores was expected to include 60% of sudden infant deaths and hence have a relative risk 8.6 times the remainder. A similar analysis by Kraus *et al.*² using linked birth and death registration data for white children in California apparently gave a generalised squared distance of 0.8 which would imply that the relative risk of the corresponding high risk group would be 4.5. Shrinkage³ may be expected to reduce the relative risks in practice.

A prospective study was set up as follows. The discriminant scores of all babies born in a defined area to be evaluated within 24 h of birth; scores larger than 85% quantile defined group A and the remainder group B. Half group A, selected at random, together with samples of group B were invited to participate in the study. This comprised an initial clinical examination made within 48 h of birth, a second at 5 weeks, together with 10 visits to the home spread over the first 20 weeks of life by specially appointed health visitors. The study started in January 1973.

During 1973, 6,003 births were screened, 19 more than the number of births registered in the area for the year. The results were as shown in Table 2. The observed relative risk for those in group A not selected for study is 6.1 which is significantly greater than 1.0, $0.005 > P$. The risk of the group who did not participate is higher and also significant. There are encouraging indications that the study may be preventing some deaths. This agrees with case reports. Hospital admission rates confirm that group A is a high risk group.

We conclude that a large scale study of all forms of post-neonatal infant mortality along these lines is feasible, and offers the best method of reducing these deaths. Meanwhile our study continues.

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Table 1 Variables included in the best linear discriminant function and the sign of the coefficient

Sign of coefficient	Variable	
—	Mother's Age	} Together the most powerful discriminators
+	Birth Order	
—	*A	} Blood group of mother*
+	*O	
+	*B or AB	
—	*Intention to breast feed	
—	Duration of 2nd stage of labour	
+	*Urinary infection	} during pregnancy
+	*Polyhydramnios	
+	*Infant premature (< 2,500 g and (or) < 37 week gestation)	

* Scale: yes = 1, no = 0.

Thegosis in herbivorous dinosaurs

THE name thegosis was coined by Every and Kühne¹ for the short and powerful process of tooth sharpening which is accomplished in mammals by the grinding of one tooth against another. Thegosis produces sharp-edged, planar (or curved planar) wear surfaces on the teeth. The thegosis wear

facets cut straight across boundaries between dentine and enamel and are typically marked with deep parallel striations (not necessarily coincident with the maximum slope of the wear facet). In some mammals thegosis keeps certain teeth sharply honed for use as weapons (as with the canines of suids and hippopotamids); in others thegosis sharpens the teeth which deal with food (as with the carnassial apparatus in felids).

In mammals thegosis wear is accompanied by a second type of tooth wear, dental abrasion, which occurs at food/tooth interfaces during mastication. Areas worn by abrasion are not sharply defined and have an irregular topography which more or less follows the original form of the tooth. In abraded areas the dentine is excavated to leave the more resistant enamel as a rounded wall and there are deep and shallow scratches without preferred orientation. During mastication the thegosis wear facets suffer abrasion; eventually they need to be recut by thegosis.

Tooth sharpening is not exclusive to mammals. Some herbivorous reptiles (notably ornithischian dinosaurs) seem to have sharpened the teeth by thegosis-like grinding, in spite of the fact that there was rarely any consistent pattern of occlusion. Two types of tooth wear in ornithischians are counterparts of thegosis wear and abrasion wear in mammals. Though the thegosis wear facets of ornithischians seem to differ from those of mammals in lacking deep parallel striations, it is evident that a process of tooth sharpening which closely resembled mammalian thegosis did operate in ornithischians and in some other herbivorous reptiles. Lack of striations from the thegosis wear facets of reptiles might be explained by assuming that active thegosis was a relatively infrequent occurrence. Then, in the long intervals between episodes of tooth sharpening, any striations would have been obliterated by abrasion wear. This is exactly the system of tooth wear which Every and Kühne describe¹ in the Eocene tapiroid *Lophiodon*. Tooth sharpening in herbivorous reptiles may not have been exactly comparable with tooth sharpening in mammals (particularly in view of reptilian polyphyodonty), but the mechanisms produce such similar patterns of tooth wear that I feel justified in referring to both as thegosis.

Before examining dental abrasion and thegosis in reptiles it is necessary to mention a third type of tooth wear which occurs in some ornithischians. This is wear caused by interdental pressure (Fig. 1a). Wear facets produced by interdental pressure are sharply defined, small in area, rounded in shape, and have flat or slightly irregular surfaces. These facets of this type are developed where the teeth in juxtaposition surface of the tooth crown, though they may sometimes be found on the lateral or medial surface. Wear facets of this type are developed where the teeth in adjacent alveoli are in contact and they are commonest where the teeth are crowded into the jaw bones and have an overlapping arrangement². Wear facets produced by interdental pressure are concealed in the intact dentition and can be seen only when the teeth are separated.

Blunting of the tips, edges, denticles, cingula and wear facets of the teeth in ornithischians is evidently the product of abrasion (Fig. 1b). Comparable tooth wear is doubtless universal among reptiles.

The literature dealing with the teeth in living and fossil reptiles gives the impression that thegosis wear is best developed (or at least best documented) in the ornithischian dinosaurs. Thegosis wear (though not identified as such) definitely occurs in some other herbivorous reptiles—in sauropods³ and in certain lizards⁴—and might well be expected to occur in some of the prosauropods, therapsids and pareiasaurs. I can find no evidence that the teeth were ever sharpened by thegosis-like grinding in omnivorous and carnivorous reptiles.

Few herbivorous dinosaurs used the teeth as sabre-like slashing weapons, analogous to the canine teeth of suids,

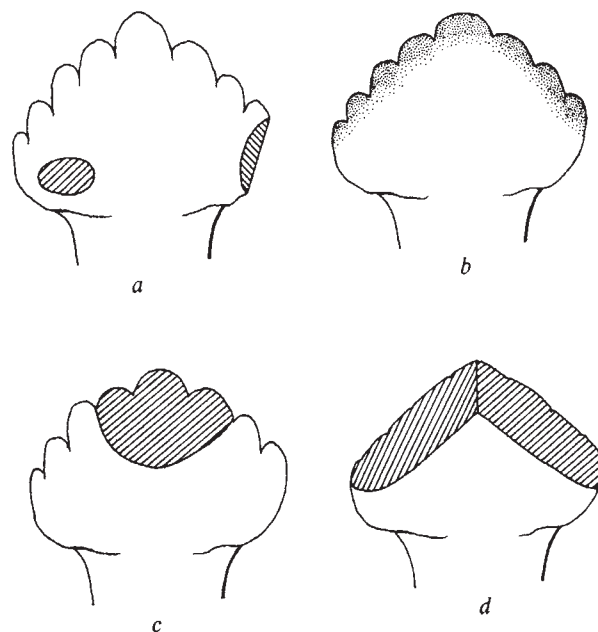


Fig. 1 Outline sketches of ornithischian teeth to show different types of tooth wear. a, Small, rounded and sharply-defined facets produced by interdental pressure; b, ill-defined areas of abrasion wear (stippled); c, single, large and sharply-defined facet produced by thegosis; d, pair of large sharply-defined facets produced by thegosis. Loosely adapted from illustrations in Thulborn^{2,15}.

tayassuids and tragulids, but this is almost certainly the function of the caniniform tusks in heterodontosaurid ornithopods⁵. In heterodontosaurids the tusks could not have been honed by tooth-on-tooth wear⁵ and their slashing edges are finely serrated instead⁶⁻⁸. No reptiles, living or extinct, seem to have employed thegosis to maintain dental weapons in fighting trim, and I conclude that herbivorous dinosaurs used thegosis solely to sharpen the edges of those teeth which dealt with food materials.

In some ornithischians thegosis wear (or a very similar type of tooth wear) was developed on a large scale: planar wear surfaces were formed along entire sections of the cheek dentitions in heterodontosaurids⁵⁻⁸, hadrosaurs⁹, ceratopsians¹⁰⁻¹² and some protoceratopsians¹²⁻¹⁴. In most ornithischians, however, thegosis wear facets were developed on individual teeth: single or paired facets (Figs 1c, d) are found in the teeth of fabrosaurids¹⁵, hypsilophodontids^{2,13,16}, pachycephalosaurids^{13,17}, some protoceratopsians^{13,18}, iguanodontids (*sensu lato*)^{13,19-21}, psittacosaurids^{13,22}, ankylosaurs^{13,23} and stegosaurs^{13,24}. A single wear facet (Fig. 1c) indicates that the tooth was sharpened directly against a single counterpart tooth in the opposing jaw; paired wear facets (Fig. 1d) were produced when the tooth interlocked with a pair of teeth in the opposing jaw¹⁵. Both single and paired facets may occur in members of a single species¹⁵.

Recognition of thegosis (or, at least, of a process closely akin to mammalian thegosis) in herbivorous dinosaurs warrants some reconsideration of tooth function in these animals. Evidently the sharp tooth edges and the planar wear surfaces produced by thegosis played important parts in mastication. The planar wear surfaces effectively reduced the tooth crowns to wedges, and as these were driven into the food they splayed it open and, eventually, divided it into two pieces. By sharpening and re-sharpening the leading edges of the wedge-like teeth—thegosis enhanced and maintained the food-cutting action of the dentition. Any grinding of food between the thegosis wear facets of opposing teeth would have been incidental to this food-cutting process. It cannot be emphasised too strongly that thegosis was not directly involved in mastication: the process of thegosis merely shaped the teeth for use as tools

in mastication. In short, the cheek teeth of many herbivorous dinosaurs might best be envisaged as chopping or cutting tools, rather than as grinders.

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Echolocation of insects by horseshoe bats

MOST bats of the Suborder Microchiroptera use echolocation during the pursuit of insect prey¹. This conclusion was originally based on observation that bats emitted high frequency orientation sounds during pursuit of insects and that their repetition rate increased sharply during close pursuit manoeuvres. Experiments in controlled laboratory conditions later demonstrated that little brown bats (*Myotis lucifugus*) could capture fruit flies (*Drosophila sp.*) by echolocation when vision and passive hearing of insect flight sounds were not possible².

This does not mean, however, that all insectivorous bats necessarily employ echolocation to the exclusion of other methods for locating insect prey. Indeed, Moehres³ observed that bats were attracted by the buzzing sound of insects which were not visible and probably not detectable by echolocation. Kolb⁴ has demonstrated experimentally that the European *Myotis myotis* commonly detects non-flying insects by passive hearing. Recently, Kolb⁵ suggests that olfaction plays an important role in food location, and that pulses of high frequency sound are accompanied by air currents which stir up odours. But the data Kolb presents do not conclusively show whether the bats located the food by scent or by echolocation.

Airapetjantz and Konstantinov⁶ have recently reported that in a large outdoor flight cage horseshoe bats of the genus *Rhinolophus* used echolocation to detect only stationary insects suspended by threads. The bats seemed to cease emitting high frequency orientation sounds when a tethered moth moved its wings and made limited flights within the cage. This report is so sharply at variance with extensive observations of many species of bats in both temperate and tropical latitudes that further investigation is clearly necessary.

Although horseshoe bats have been intensively studied in the laboratory, their insect pursuit behaviour has not been observed in natural conditions with appropriate acoustic apparatus. We were able, however, to study a small colony of *Rhinolophus ferrum-equinum* which has roosted for many years in the principal buildings of the Cimiterio Suburbano in Pisa. Thanks to special permission from the municipal authorities we were able to observe and record these bats during many evenings in June 1973 as they flew out of one building and hunted insects along the pathways of the cemetery and close to the walls of several other structures.

Our portable, battery-operated apparatus consisted of plastic dielectric microphones and the amplifier-detector circuit described by McCue and Bertolini⁷. The amplified ultrasonic signals were recorded on a Pemco Model 110A instrumentation tape recorder and monitored with a small battery-operated oscilloscope (Tektronix type 323). Almost all of the horseshoe bats disappeared after the first 20–30 min of each evening's foraging flights. We could not ascertain whether they flew away from the cemetery or landed, possibly with full stomachs as is frequently the case with insectivorous bats during the summer months when food is plentiful. Most flew along a predictable flight path each evening between vertical stone walls and rows of cypress trees whose branches were about 0.5–2 m from the walls. On most evenings we placed a Holgate ultrasonic detector⁸ 20–30 m 'upstream' from the position we had selected for tape recording. The audible beat notes from this heterodyne detector alerted us as horseshoe bats approached and allowed us to concentrate attention on them rather than the numerous vespertilionid bats (probably *Pipistrellus pipistrellus*) which were also abundant in the vicinity.

While many horseshoe bats flew rapidly past our position without slowing or turning, and thus were probably not hunting, many others seemed clearly to be pursuing insects such as moths of 1 to 2 cm wingspread which were often present. On several occasions a bat would circle very rapidly around a cypress tree, flying within a few centimetres of its outer branches, and we strongly suspect that at these times they were pursuing and sometimes capturing insects that had been resting on the outer twigs. These trees were 0.5–1.5 m in diameter at the altitudes where this circling behaviour occurred.

On some evenings we attempted to elicit more insect pursuit manoeuvres within range of our microphones by presenting small tethered insects attached by light threads to a fishing pole. These were manoeuvred into the customary flight path of the bats and caused to move as nearly as possible in a normal fashion. Two or three were repeatedly attacked.

On several dozen occasions during the last two weeks of June we were able to observe flight manoeuvres that resembled insect pursuit, although it was not possible to be certain in all cases that it was an insect rather than the cypress twigs or our poles and thread that was attracting the bats' attention. Many of these were spontaneous manoeuvres when no pole or tethered insect was present while others seem directed at our tethered insects. In none of these cases was there the slightest sign that emission of orientation sounds ceased. On the contrary, their repetition rate increased as has been repeatedly observed with other insectivorous bats both in the laboratory and in natural conditions. Every time a horseshoe bat flew within reasonable range of the microphone, typical orientation sounds were emitted at characteristic repetition rates. When the bats made rapid turns, dodged our poles, or seemed interested in insects, there was always a marked increase in repetition rate.

Preliminary analysis of our tape recordings shows approximately the same physical properties of the orientation sounds as have been described for the same species dodging

wires in a relatively small laboratory room. Whenever the signal-to-noise ratio was reasonably adequate both rising and falling frequencies were distinctly visible at the beginning and end of each pulse when the output of a period meter was displayed on a cathode ray oscilloscope^{9,10}.

It seemed worthwhile to analyse in some detail pulse durations and interpulse intervals in four cases when a single horseshoe bat yielded good recordings continuously for a few seconds and during that time engaged in what seemed to be an insect pursuit. Typical pulse durations when flying reasonably straight without apparent pursuit manoeuvres were 50–75 ms, but occasional pulses had clearly defined durations as long as 85 or 90 ms. These were single pulses at reasonably high signal-to-noise ratios without any interruptions. During 'buzzes' on close approach to an insect or other small object pulse durations dropped to about 10 ms and in one case to 7–8 ms. The short series of pulses, having durations of 10–15 ms, lasted for only about 0.1–0.2 s. Interpulse intervals were almost always shorter than pulse durations, and they decreased to approximately 5 ms during the buzzes. Occasionally relatively long pulses were interrupted by intervals as short as 2 or 3 ms. Similar patterns have often been observed in the laboratory.

Thus all the greater horseshoe bats we were able to observe closely while apparently hunting insects under natural conditions emitted intense and rapidly repeated orientation sounds and gave every evidence that they were employing echolocation to locate and intercept their insect prey.

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Olfactory imprinting resulting from brief exposure in *Acomys cahirinus*

RECENT experimental studies of olfactory 'imprinting' in infant mammals have typically utilised relatively long term exposure to the training odour, during which that odour could become associated with such conventional reinforcers as food and warmth^{1–6}. Here we report an instance of mammalian olfactory imprinting which is truly analogous to classical avian imprinting, that is, the imprinting exposure being of a relatively short duration with no readily identifiable conventional reinforcer being present at the same time with the imprinted odour. The subject species, *Acomys*

cahirinus (spiny mouse), is a murid rodent whose precocial infants possess functional motor and sensory capabilities within hours of birth^{7,8}.

An initial experiment was conducted to ascertain whether infant *Acomys* would become attached to artificial olfactory cues associated with their cage—their home environment. As soon as a newly-born litter was discovered (about 1–12 h after birth), the parents and infants were placed together in a clean cage containing a shallow layer of bedding material overlying a level teaspoon of either ground cinnamon (Cin) or ground cumin (Cu) which had been evenly sprinkled over the bottom of the cage before the introduction of the bedding material. The animals remained in this cage in an isolation room until testing 24–26 h later—separate rooms being used for the two exposure odours. A total of 12 litters (34 young) were randomly assigned to the two exposure conditions; with seven litters (18 young) exposed to Cu, and five litters (16 young) exposed to Cin. An earlier control study had indicated that naive 1-d-old *Acomys* young show no inborn preferential response to either of the test odours.

After the 24–26 h exposure period (at 26–36 h old), the young were individually tested in a series of two-choice preference tests with Cin and Cu soiled bedding simultaneously present at opposite ends of the test cage. A young mouse was placed on a clean starting strip centred between the two areas of odourised bedding material and observed until moving entirely onto one of the areas of bedding, or until a maximum of 300 s had elapsed without a choice being made. Each young was given 10 successive two-choice preference tests in this manner.

A preference score was calculated for each subject by subtracting the number of positive responses to Cu from the number of responses to Cin. Thus, a positive score would indicate a preference for Cin over the 10 consecutive choice tests, while a negative score would indicate a preference for Cu. The 18 young that had been exposed to Cu had a mean preference score of –2.61. A Wilcoxon matched-pairs signed-ranks test on the individual preference scores indicated that the preference for Cu (the training odour) was significant $P < 0.02$ (two-tailed test). Likewise, the 16 young exposed to Cin showed a subsequent preference for that odour during the choice tests—mean preference score = +4.50 ($P < 0.01$, two-tailed Wilcoxon test).

Having ascertained that infant *Acomys* young prefer a chemical stimulus to which they had been exposed for 24 h (in their home cage) over a novel chemical stimulus, we next wished to determine whether conspecific young would show similar preferences as a function of a relatively brief exposure period during which the chemical stimulus would not be associated with any conventional reinforcer. This was investigated by exposing *Acomys* young 2–12-h-old to the odour of either Cin or Cu for a single period of 1 h, and individually testing them in a series of two-choice preference tests (as above) 24 h after the exposure period.

During the exposure session, all of the young from a given litter were removed from the home cage and parents and placed together into an acrylic cylinder (exposure chamber). A second cylinder (odourant chamber) containing a teaspoonful of the appropriate training substance (either Cin or Cu) was linked to the exposure cylinder by neoprene tubing (18 inches long) with a filter placed over the end entering the odourant chamber. Air was forced from the odourant chamber, through the filter and tubing, and into the exposure chamber; thereby exposing the young to the airborne odour of either Cin or Cu. The young were returned to the home cage immediately following the exposure period, where they remained until testing 24 h later. A total of 29 young mice (from 12 litters) were used in this experiment, with 15 being exposed to Cin and 14 to Cu.

A statistical analysis of the preference scores for all 29

young indicated that the exposure odour was preferred significantly over the novel odour during the choice tests ($P < 0.01$, two-tailed Wilcoxon test). Further analyses indicated that the mean preference score of the 15 young exposed to Cin was $+2.13$ ($P < 0.025$, one-tailed test) and -1.86 for the 14 young exposed to Cu ($P < 0.025$, one-tailed test). Thus, the exposure odour was preferred over the novel odour—regardless of whether the young mice had been exposed to Cu or Cin.

The survival value of such rapidly acquired stimulus preferences in this precocial murid rodent would seem to be similar to that of imprinting in avian species. In each instance, early attachment to a specific stimulus complex would serve to decrease the likelihood of the neonate wandering away from the parental figure or home area, and thereby decrease the possible risks of predation, starvation, or exposure to the elements. While precocial avian species tend to rely primarily upon visual cues for early stimulus attachments⁹ precocial species of macrosomatic mammals (such as *Acomys*) might be expected to rely primarily upon olfactory cues to mediate early attachments^{1,6,10,11}. There is, however, some evidence to suggest that other sensory modalities may function to some extent in attachment formation of both precocial avian and macrosomatic mammalian species. Gottlieb¹², and Porter and Stettner¹³, for example, report that hatchlings of several species of precocial birds become attached to specific auditory signals as well as visual cues; while Sluckin¹⁴ has found that visual imprinting may occur in guinea pigs. Thus, even during the first few days of life, stimulus attachments and preferences in these species are possible in other than the most salient sensory modality.

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Evidence for a dual central role for angiotensin in water and sodium intake

ANGIOTENSIN II induces short-latency water intake when infused intravascularly or injected into certain brain regions of mammals^{1,2}. But conceptual difficulties arise if one asks why this should be so, and whether the data reflect real physiological actions. For example, angiotensin is a pressor hormone formed from kidney-based renin in response

to challenge such as hypotension and hypovolaemia^{3–7}. Water ingestion, in itself, is not an adaptive response to such challenges, since most ingested water is distributed intracellularly and will not relieve a vascular crisis. An adaptive response to hypotension or hypovolaemia would involve ingestion of an isotonic mix of fluids, since this would most rapidly and effectively increase vascular volume. In fact, hypovolaemia does result in an immediate increase in preference for isotonic saline over water and a delayed (6–10 h) acceptance of unpalatable hypertonic salt solutions^{8,9}. But, a possible involvement of angiotensin as a rapid and direct facilitator of sodium intake (apart from a slow and indirect role through stimulation of aldosterone release) has not yet been reported and some evidence suggests that angiotensin may not play any significant role in regulating sodium intake in the rat^{10–12}.

We now present data indicating that angiotensin can rapidly facilitate Na^+ intake, resulting in selection and ingestion of a mix of water and electrolytes best suited to overcome deficits in circulatory volume or pressure.

Adult male rats of the Long-Evans strain, weighing 225 to 300 g, were anaesthetised with Nembutal and stereotactically implanted with 23 gauge cannulae in lateral preoptic nucleus, nucleus accumbens, or lateral cerebral ventricles. One week was allowed for recovery from surgery; during this time animals were individually housed with free access to food pellets and deionised water as well as the saline solution with which they would later be tested. Testing was conducted in the home cages with the positions of the water and saline drinking bottles kept constant. Angiotensin and carbachol (another central dipsogen¹³) were prepared with isotonic saline vehicle to a concentration of $500 \text{ ng } \mu\text{l}^{-1}$ and $1 \text{ } \mu\text{g } \mu\text{l}^{-1}$ respectively. Intracranial injections were of $1 \text{ } \mu\text{l}$ volume and ventricular infusions of angiotensin were carried out at a rate of $500 \text{ ng } \mu\text{l}^{-1}$ per 8 min over an 8 h period.

The effects of several thirst-inducing stimuli on intake of water and 1.8% saline (two-bottle choice tests) were observed in rats in normal water and sodium balance during a 1 h test period. In 32 rats, intracranial injection of angiotensin resulted in an average intake of 9.6 ml of water and 6.8 ml of 1.8% saline. Following carbachol, 15 animals ingested an average of 9.5 ml of water and only 0.5 ml of 1.8% saline. In 14 other rats, thirst was induced by subcutaneous injection of 5 ml of 1.5 M NaCl. Average fluid intakes after this intracellular dehydration were 21.7 ml of water and 0.9 ml of 1.8% saline. Thus, thirst induced by intracellular dehydration or by central cholinergic stimulation resulted in substantial intake of water only, with minimal intake of the normally non-preferred 1.8% saline, whereas central injections of angiotensin resulted in substantial intakes of both water and 1.8% saline.

If a potentiation of sodium as well as water intake is characteristic of angiotensin action, this should remain evident when animals that are deprived of water or sodium are stimulated with angiotensin. Intake of water and 1.8% saline was observed in 13 rats (1 h tests) when deprived of fluid for 24 h and when deprived of fluid for 24 h plus receiving central injections of angiotensin. Following deprivation alone, the rats consumed an average of 17.1 ml of water and 3.0 ml of 1.8% saline; following deprivation plus angiotensin, the rats consumed an average of 23.9 ml of water and 11.7 ml of 1.8% saline. Increased intake of water and saline noted with angiotensin was significant ($P < 0.01$, paired sample t test). A similar study was carried out on 10 animals, but with a 48 h period of fluid deprivation and a choice test between water and 2.7% saline. After 48 h of fluid deprivation, the average intake of water was 22.4 ml, and the average intake of 2.7% saline was 2.2 ml. After deprivation plus angiotensin, intake of water increased to 25.7 ml, while intake of 2.7% saline

increased to 6.1 ml. The increased intake of salt solution was again significant ($P < 0.01$).

We next assessed the extent to which angiotensin could potentiate an already existing sodium appetite. Ten animals were maintained on sodium deficient chow (General Biochemicals) for 7 d. Half the animals then received angiotensin intracranially and all were then given a 1 h two-bottle preference test (water and 2.7% saline). Following another week on sodium deficient diets, the testing conditions for the two groups were reversed. Angiotensin not only increased water intake, but also significantly ($P < 0.01$) increased consumption of 2.7% NaCl. (Mean intake without drug: water, 1.7 ml; saline, 2.8 ml; mean intake after angiotensin: water 9.0 ml; saline 7.5 ml.)

The same testing procedure was followed after a third and fourth week of sodium deprivation, but with injections of carbachol substituted for angiotensin. Unlike angiotensin, carbachol increased water consumption only. (Mean intake without drug: water, 2.3 ml; saline, 7.8 ml; mean intake after carbachol: water 7.7 ml; saline 5.2 ml.) In later tests after weeks 5 and 6 on a sodium-deficient diet, angiotensin still potentiated sodium intake (mean intake without drug: water, 0.9 ml; saline, 6.5 ml; mean intake after angiotensin: water 7.9 ml; saline, 10.4 ml). The key point is that angiotensin, but not carbachol, markedly increased the sodium intake of rats already manifesting a sodium appetite, while both drugs enhanced water intake.

The preceding experiments all show that discrete injections of angiotensin into the brain result in ingestion

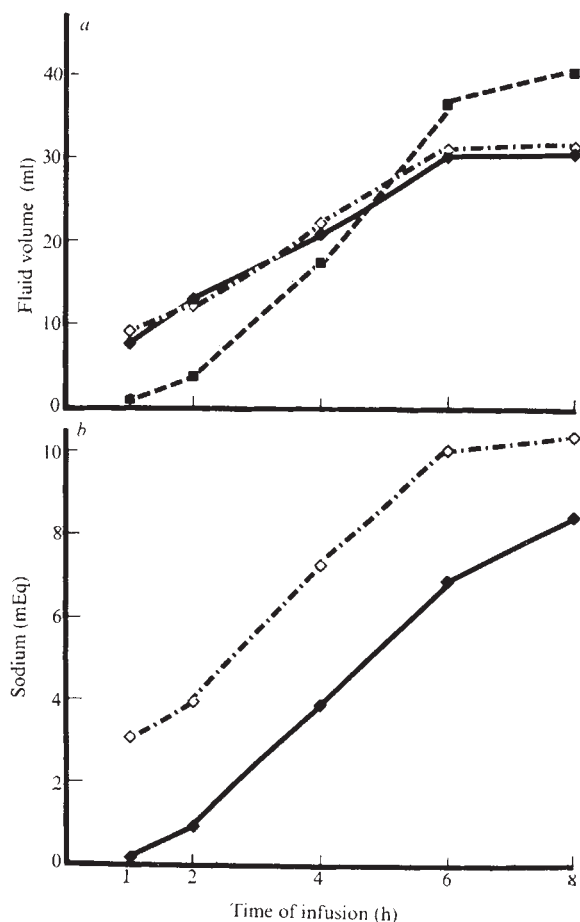


Fig. 1 *a*, Mean intake of $\blacklozenge$ — $\blacklozenge$ water and $\diamond$ — $\cdots$ — $\diamond$ 1.8% NaCl and urine losses ($\blacksquare$ — $\cdots$ — $\blacksquare$) of seven rats during ventricular infusion of angiotensin at a rate of 500 ng per μ l per 8 min. *b*, $\diamond$ — $\cdots$ — $\diamond$ Sodium intake; $\blacklozenge$ — $\cdots$ — $\blacklozenge$ sodium out; sodium content of urine was determined by flame photometry.

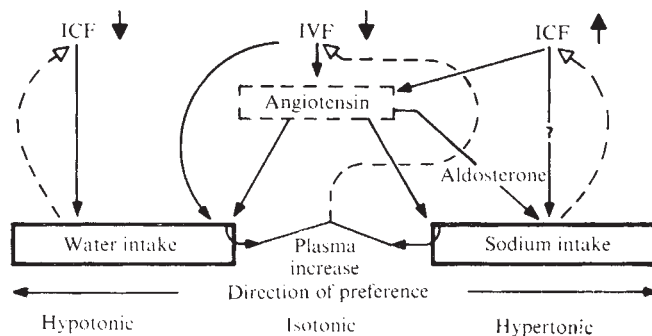


Fig. 2 Model of central control of thirst indicating angiotensin effect on both water and sodium intake, ICF $\downarrow$ —: intracellular fluid decrease (and/or Na^+ increase) in monitor neurones; ICF $\uparrow$ —: intracellular fluid increase (and/or Na^+ decrease) in monitor neurones; IVF $\downarrow$ —: intravascular fluid volume (and/or pressure) decrease; solid line and arrow =: facilitatory effect; dashed line and open arrow =: inhibitory (negative feedback) effect.

of saline solutions as well as water when both are available. Conditions leading to increases in endogenous renin-angiotensin levels, however, often involve a prolonged enhancement of such levels. In order to simulate a prolonged enhancement of renin-angiotensin levels more closely, long-term intraventricular infusions of angiotensin were carried out on rats offered a choice of water and 1.8% saline or water and 2.7% saline. Seven rats were offered a choice of water and 1.8% saline during the 8 h infusion period (Fig. 1). Drinkometer records indicated that both water and saline intake occurred early in the first hour and intake of each fluid alternated throughout the infusion period so that an isotonic mix was self selected. Sodium losses in urine did not at any time exceed oral intake of sodium. Six rats were offered a choice of water and 2.7% saline during the infusion period. Total average intake was 44.6 ml of water and 15.4 ml of 2.7% saline, with ingestion of each fluid beginning within the first hour. Again, sodium losses in urine did not exceed oral sodium intake.

These results imply that the drinking behaviour induced by angiotensin is qualitatively different than the thirst induced by carbachol, or by intracellular dehydration. In both sated animals and in animals with a pre-existing fluid or sodium deficit, intracranially administered angiotensin facilitates intake of sodium solutions as well as water, thus making the ingested fluid more appropriate for repairing deficits in the extracellular fluid compartment.

A model encompassing these observations is illustrated in Fig. 2 (ref. 14). Intracellular dehydration activates a thirst excitatory system which leads to water intake preferentially. This system seems to be mediated in part by cholinergic neurones in the rat¹⁵. Activation of this thirst system, through intracellular fluid dehydration with hypertonic saline injections or centrally with carbachol, does not lead to appreciable sodium intake. Chiarviglio and Taleisnik have reported that activity in cholinergic systems actually may inhibit sodium intake, while cholinergic blockade facilitates sodium intake¹⁶.

Intravascular fluid depletion, on the other hand, is depicted as activating neuronal systems which facilitate sodium intake as well as water intake, although acceptance of highly aversive concentrations of sodium (that is sodium appetite) occurs only after a delay of 6–10 h following a challenge. Since sodium intake induced by hypovolaemia remains in the adrenalectomised rat¹⁷, aldosterone cannot exclusively mediate sodium appetite; several other factors, including baroreceptor input and angiotensin, might have a more immediate effect on intake of sodium. Our data

suggest that angiotensin is one of the factors directly influencing the intake of sodium as well as water.

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Exchange of neurotransmitter amino acid at nerve endings can simulate high affinity uptake

AXELROD¹ found that released noradrenaline is recaptured by presynaptic nerve terminals, and proposed reuptake as a mechanism for rapid neurotransmitter inactivation. Subsequent studies led to the identification of high and low-affinity components in the uptake of several putative neurotransmitters by nerve terminals²⁻⁷. Although the apparent K_m values reported for the high-affinity uptake of some neurotransmitters (notably amino acids) are comparable to those reported for the low-affinity uptake of other neurotransmitters, it is generally thought that the inactivation of most neurotransmitter amino acids is obtained through high-affinity uptake systems having a K_m of the order of 10^{-5} M. Indeed, the existence of a high-affinity uptake for a given substance is often considered to favour its being a neurotransmitter.

High-affinity uptake systems for neurotransmitter amino acids have been demonstrated by methods in which high tissue: medium ratios of radioactivity, simulating net uptake, might have been obtained by homoexchange^{8,9}. So far this possibility has been investigated, by ourselves, amongst others¹⁰⁻¹², by methods that could not give a satisfactory answer.

We have now explored the possibility that GABA, at concentrations used for studies on high-affinity uptake, can release GABA from the endogenous pool.

It seems that exchange can largely account for what has previously been interpreted as uptake. Purified synaptosomes¹³ were incubated in the presence of a very low concentration of ³H-GABA to label the endogenous pool, without altering its size significantly. Aliquots were then superfused with regular medium, which was replaced after few minutes by identical medium containing varying concentrations of GABA. The superfusion apparatus, which largely

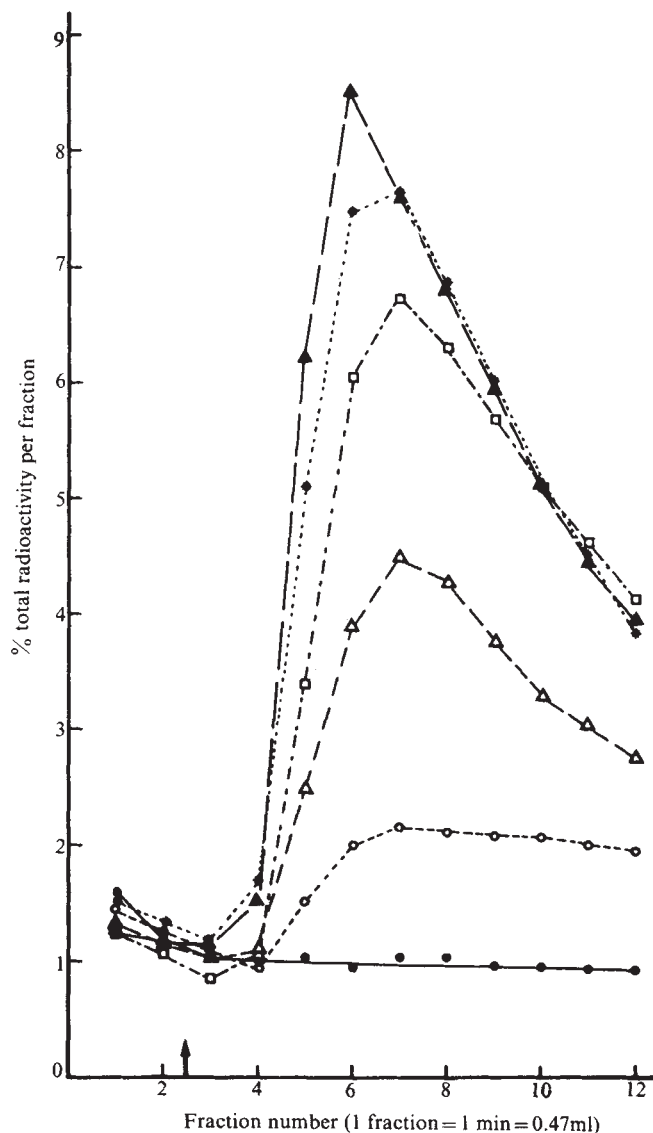


Fig. 1 Stimulation of ³H-GABA release from synaptosomes by different concentrations of unlabelled GABA. Purified synaptosomes¹³ from adult rat cerebrum were resuspended in 0.32 M glucose, at a protein concentration of 5 mg ml⁻¹. Aliquots were diluted 1:10 in Krebs-Ringer medium¹⁴, after 15 min equilibration at 37° C in a rotary waterbath, a small volume (1/100 of the final volume) of a solution containing 50 μM 2, 3-³H-GABA (New England Nuclear Corporation, specific activity 10 Ci mmol⁻¹) was added to the incubation flasks. After an additional 10 min, 1 ml aliquots of the suspension were placed on Millipore filters (0.65 μm pore) lying at the bottom of six parallel superfusion chambers¹⁴, the filters were washed, 3 ml of prewarmed, oxygenated, glucose-containing medium were added to each chamber, and the superfusion was started, at a rate of 0.47 ml min⁻¹ (ref. 14). After 5.5 min, 20 ml of medium containing varying concentrations of GABA were added to the chambers (arrow) and superfusion was stopped at 15 min. Fractions were collected every minute; the radioactivity of the effluent and that remaining on the filters was measured by liquid scintillation. All the solutions contained 0.1 mM amino-oxyacetic acid to prevent GABA metabolism. In these conditions, over 90% of the radioactivity was recovered as unchanged ³H-GABA. These and subsequent experiments run without amino-oxyacetic acid gave qualitatively similar results, but a significant amount of ³H-GABA metabolites was recovered. The radioactivity recovered in the first three fractions was at times more erratic, and is not presented. The radioactivity found in each fraction is given as a percentage of the total radioactivity recovered (filter plus total fractions). Each curve is the average of three experiments. ▲, 1 mM GABA; *, 100 μM GABA; □, 50 μM GABA; △, 10 μM GABA; ○, 1 μM GABA; ●, control.

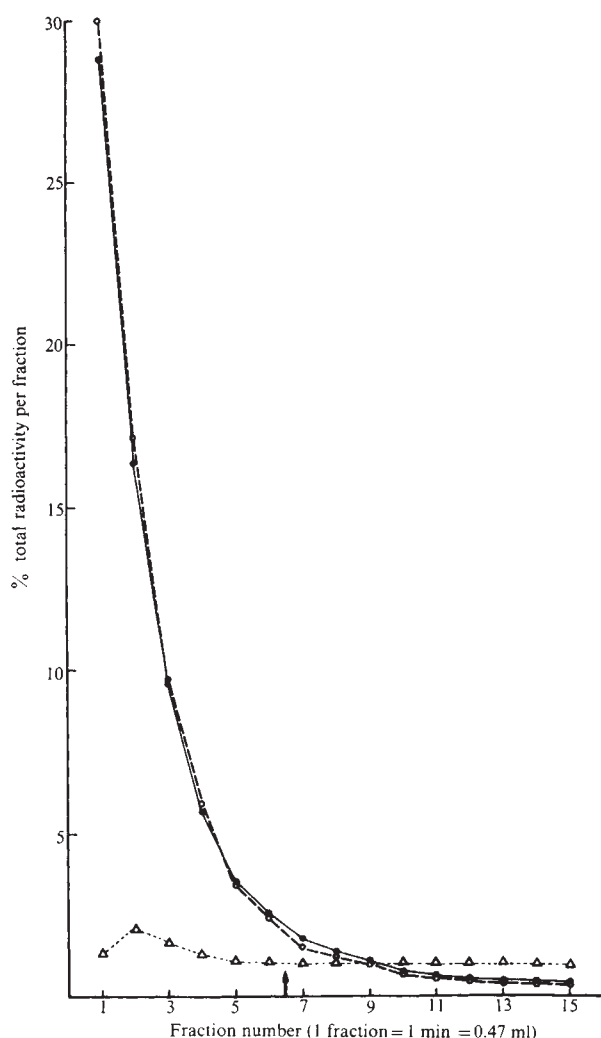


Fig. 2 Effect of sodium deprivation on the release of ^3H -GABA from synaptosomes. Experimental conditions as described in the legend for Fig. 1, except that the medium used for superfusion contained 0.256 M sucrose instead of 0.128 M NaCl. The figure shows the radioactivity recovered in all the 15 fractions collected. The addition of 0.5 mM GABA to the Na^+ -free superfusion fluid had no appreciable effect on the release of ^3H -GABA. Other concentrations of GABA that were tried (10, 100 and 1,000 μM) were also ineffective. Each curve is the average of two experiments. $\circ$, Na^+ -free, 0.5 mM GABA; $\bullet$, Na^+ -free; $\triangle$, control.

prevents reuptake, is described elsewhere¹⁴. Superfusion with unlabelled GABA caused an immediate, dose-dependent increase in the efflux of ^3H -GABA (Fig. 1). The release was about doubled by 1 μM GABA and was increased several fold by a concentration of 10 μM ; both concentrations are in the range of the high-affinity uptake system^{4,6}. The radioactivity released reached a peak after a few minutes and then

decreased, because of dilution of the synaptosomal ^3H -GABA by unlabelled GABA entering the tissue. The stimulation of ^3H -GABA release showed a substrate specificity similar to that described for uptake. Among the various compounds tested, only γ -amino- β -hydroxybutyric acid was a strong stimulator of ^3H -GABA release (Raiteri *et al.*, unpublished). Homoechange and heteroexchange of amino acids at millimolar concentrations has already been shown in brain slices^{15,16}.

On the basis of an endogenous GABA level of 19 ± 4 nmol per mg synaptosomal protein (G. L., and M. R., unpublished) and assuming that the ^3H -GABA is homogeneously mixed with the endogenous pool, the rates of ^3H -GABA release can be calculated from the percentage of radioactivity released at the peak of the curves (taking the immediate prestimulation level of radioactivity as 100%). These rates are comparable with the initial rates of GABA high-affinity uptake obtained in a previous study⁶. In particular, the release rate at a saturating GABA concentration (1 mM) was similar to the apparent V_{max} of the high-affinity uptake system. In some experiments, in which ^3H -GABA release was stimulated by adding 1 or 10 μM ^{14}C -GABA to the superfusion fluid, to measure the uptake of ^{14}C and the release of ^3H simultaneously, the calculated ^3H -GABA efflux was similar to the influx of ^{14}C -GABA. Even considering the approximation introduced by the calculation, these data suggest that homoechange accounts for at least a large part of the radioactive GABA entering synaptosomes by the so called high-affinity uptake system. In the concentration range of the low-affinity system, however, the influx of ^3H -GABA (ref. 6) was greater than its calculated efflux, indicating that a net uptake of the amino acid took place.

It is known that GABA uptake is sodium-dependent¹⁷⁻¹⁹. We previously showed that the high-affinity uptake of GABA detectable in embryonic chick brain slices is more sodium-dependent than the low affinity uptake¹⁹. Sodium deprivation also seems to inhibit the high-affinity more than the low-affinity synaptosomal uptake of glutamate, aspartate, glycine⁷ and GABA (G. L., and M. R., unpublished). Figure 2 shows a rapid depletion of synaptosomal GABA content upon superfusion with sodium-free medium. Over 50% of ^3H -GABA present was released in 2-3 min and the addition of GABA (10-1,000 μM) to the superfusion fluid did not appreciably alter the release pattern. Extensive release and absence of any detectable homoechange could well account for what looks like an almost complete inhibition of the high-affinity uptake of GABA.

If glycine behaved like GABA, then the exchange of glycine at low concentrations should be detectable in synaptosomes from the spinal cord, medulla and pons (where a high-affinity uptake system for glycine was described^{5,7} and where this amino acid acts as a neurotransmitter^{20,21}), but not in synaptosomes from the cerebral cortex (where only a low-affinity uptake system for glycine was detected^{5,7}). Figure 3 shows that synaptosomes from spinal cord and brain stem do indeed exhibit a dose-dependent increase in the release of ^3H -glycine upon superfusion with 10, 25 and 100 μM glycine. In contrast, cortical synaptosomes did not respond to the addition of glycine at concentrations of 10 and 25 μM , which are both in

Table 1 Changes in the levels of GABA and of radioactivity in media after incubation

Original concentration (μM)	0	1	5	10
% change in radioactivity		-49 (2)	-46 (2)	-36 $\pm$ 5 (6)
Concentration expected (μM)		0.5	2.7	6.4
Concentration found (μM)	1.3 $\pm$ 0.3 (6)	2.1 $\pm$ 0.3 (5)	5.5 $\pm$ 0.3 (6)	9.6 $\pm$ 0.9 (12)

Synaptosomes from rat cerebrum, resuspended in 0.32 M glucose at a protein concentration of 4 mg ml⁻¹ were diluted 1 : 10 in Krebs-Ringer medium and equilibrated at 37°C for 15 min in a rotary waterbath. Then, a small volume (1/100 of the final volume) of a solution of ^3H -GABA was added, to give the final concentration reported in the first line. After 10 min incubation, the suspension was either filtered through 0.45 μm Millipore filters or centrifuged for 10 min at 10,000g. The radioactivity was measured in the filters (or pellets) and in the filtered medium (or supernatant). The concentration of GABA present in the medium after incubation was measured by an assay to be described elsewhere. Some data obtained by this assay were checked by a double isotope dansyl derivative method²⁵, which gave essentially identical results.

Means $\pm$ s.d. are presented. The number of experiments is given in parentheses.

the range of the high affinity uptake system^{5,7}, and responded only weakly to a concentration of 100 μM .

In a set of typical uptake experiments run at low amino acid concentrations, we measured concentration and radioactivity of ^3H -GABA in incubation media before and after incubation. In the presence of exchange, the decrease of concentration observed after incubation should be less than that of radioactivity. Table 1 shows that a large part of the radioactivity originally present in media containing 1, 5 or 10 μM ^3H -GABA was taken up by synaptosomes. Changes in concentration of GABA showed a different pattern. With 1 or 5 μM GABA there was an actual gain in concentration, and with 10 μM GABA a barely detectable, not significant decrease in concentration was observed. If one takes into account the 1.3 nmol ml⁻¹ of GABA appearing in the medium in the absence of added GABA, the net removal of GABA which seems to take place is much lower than that expected from radioactivity measurements.

In conclusion, homoechange seems to be a major mechanism by which radioactive GABA is transported into synaptosomes when low substrate concentrations are used. A net uptake, which may or may not be of high affinity component, could be computed only after subtracting the large contribution of homoechange; therefore the problem of the existence and function of the high-affinity net uptake of GABA and, possibly, of other neurotransmitter amino acids in synaptosomes should be re-evaluated.

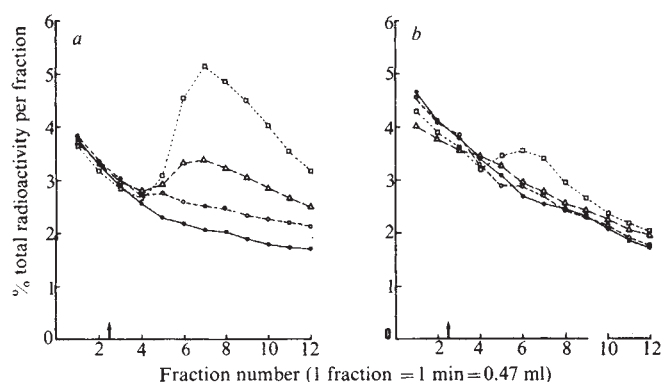


Fig. 3 Effect of different concentrations of unlabelled glycine on the release of ^3H -glycine from synaptosomes. Experimental conditions as described in the legend for Fig. 1, except that 0.5 μM 2- ^3H -glycine (New England Nuclear Corporation, specific activity 11.1 Ci mmol⁻¹) was used to label the synaptosomal glycine pool. *a*, Synaptosomes from spinal cord, medulla and pons; *b*, synaptosomes from cerebral cortex. $\square$, 100 μM Gly; $\triangle$, 25 μM Gly; $\circ$, 10 μM Gly; $\bullet$, control.

Interestingly, several properties (such as saturability and sodium-dependence) thought to be typical of GABA high-affinity uptake seem also characteristic of exchange. The utility of sodium-free media to characterise high-affinity uptake is questionable, because of the large loss of endogenous amino acid determined by this condition.

In view of our findings, it is possible that the specific labelling of certain populations of nerve endings by a given amino acid, observed in various experimental conditions^{7,24}, may occur through an exchange process. The data obtained with glycine seem to support this interpretation.

It should be noted, finally, that if reuptake by presynaptic terminals were the main mechanism of inactivation of the liberated neurotransmitter, an uptake system with a K_m of the order of 10^{-3} M (low affinity) might be as effective as one with a K_m of about 10^{-5} M. The possible contribution of post-synaptic areas and of glial cells^{22,23} to the reuptake process should also be considered.

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Stimulation of synaptosomal dopamine synthesis by veratridine

ISOLATED synaptosomal preparations maintain many of the functional properties of intact neurones¹ and the uptake of putative biogenic amine neurotransmitters such as noradrenaline, dopamine and serotonin, is well documented²⁻⁵. In addition, stimulation of synaptosomal catecholamine release has been demonstrated in response to depolarising concentrations of potassium^{4,6} or veratridine⁶, an alkaloid able to produce depolarisation in intact neurones by increasing sodium permeability^{7,8}. In intact adrenergic neurones stimulation of transmitter release is often accompanied by a concurrent increase in the rate of transmitter synthesis, possibly through a reduction in feedback inhibition of tyrosine hydroxylase⁹⁻¹³. The demonstration of a link between stimulated neurotransmitter release and stimulated synthesis in synaptosomes would be an important indication of the validity of studies of synaptosomal processes in order to gain insight into the functioning of intact neurones. We report here that striatal synaptosomes maintain the ability to respond to depolarising concentrations of veratridine with a calcium-dependent tetrodotoxin-sensitive increase in dopamine synthesis.

Male Sprague-Dawley rats (200–250 g) were decapitated and the striatum was dissected out and placed in polyethylene tubes in ice. The P_2 fraction (containing synaptosomes, mitochondria and myelin) was prepared essentially as described by Gray and Whitaker¹⁴. Most of the tyrosine hydroxylase activity in the P_2 fraction has been shown to be associated with the synaptosomal of this fraction after sucrose density gradient centrifugation¹⁵. The P_2 fraction was resuspended in a Tris-buffered incubation medium, with 15%–20% of the P_2 from one rat used for each incubation. Dopamine synthesis was measured by incubating the tissue with L-1-¹⁴C-tyrosine and monitoring the production of ¹⁴CO₂, as previously described¹⁶. Essentially all newly formed dihydroxyphenylalanine is converted to dopamine under these conditions¹⁶. Synthesis was proportional to tissue and time for at least 30 min. The uptake and efflux of L-3,5-³H-tyrosine was measured by separating the tissue from the medium on a Millipore filter, as previously described¹⁶.

To measure the effect of stimulated catecholamine release on the rate of dopamine formation, synthesis was measured during exposure to veratridine. Blaustein *et al.*⁶ have demonstrated that synaptosomal catecholamine release is increased by exposure to veratridine. As Table 1 shows, veratridine produced a 50% increase in synthesis of dopamine. In intact neurones veratridine-induced depolarisation is prevented by treatment with tetrodotoxin, which seems to block sodium entry¹⁷. Blaustein *et al.*⁶ have shown that tetrodotoxin blocks the veratridine-induced increase in synaptosomal amine release. Similarly, Table 1 shows that the veratridine-induced increase in synthesis is prevented by earlier treatment with tetrodotoxin. Tetrodotoxin alone has no effect on dopamine synthesis.

The uptake of labelled tyrosine was inhibited by veratridine—the percentage control uptake 2 and 5 min after exposure to veratridine was 67%±2% and 60%±2% respectively ($N=6$). Veratridine also stimulated the efflux of labelled tyrosine after *in vitro* labelling. The amount of labelled tyrosine remaining in the tissue 2.5 and 5 min after exposure to veratridine was 70%±3% and 65%±4% of controls, respectively ($N=6$). That both the decrease in uptake and increase in efflux of tyrosine seem to be equally affected by veratridine suggests that the specific activity of tyrosine in the tissue is not increased by veratridine; but since this preparation consists of synaptosomes from several different transmitter systems (as well as free mitochondria), measurements of labelled tyrosine uptake and efflux in the total preparation may not reflect alterations that might occur in tyrosine-specific activity in the dopaminergic synaptosomes.

It has been shown repeatedly that for transmitter release to occur from nerve endings, the presence of extracellular calcium is necessary¹⁸. This is also true for veratridine-induced synapto-

Table 2 Calcium-dependence of the veratridine-induced increase in dopamine synthesis

	Dopamine synthesis (nmol L ⁻¹ g ⁻¹)		
	--Ca ²⁺ ₃	-Ca ²⁺ + EGTA	--Ca ₃₃
Controls	13.8±0.22 (18)	13.8±0.41 (18)	12.8±0.72 (10)
Veratridine	18.1±0.30 (18)*	14.4±0.44 (18)	12.0±0.82 (10)

Aliquots of the striatal P_2 fraction were incubated for 5 min at 37°C either in control medium, Ca²⁺-free medium containing 1 mM EGTA, or simply Ca²⁺-free medium, followed by the simultaneous addition of veratridine (7.5×10^{-5} M) plus L-1-¹⁴C-tyrosine (1×10^{-5} M) or by the addition of tyrosine alone, and incubated for an additional 5 min. Values represent the mean ± s.e.m. The number of observations is in parentheses.

* $P < 0.001$ controls.

somal amine release⁶. Table 2 shows that the increase in dopamine synthesis that usually occurs in response to veratridine was prevented when calcium is omitted, with or without the chelating agent ethyleneglycol-bis-[β-aminoethylether]NN'-tetracetic acid (EGTA). It is important to note that in order to demonstrate a consistent increase in synthesis, it was necessary to measure synthesis during the initial 5-min exposure to veratridine. For example, if the tissue was preincubated for 10 min with veratridine and then labelled tyrosine was added and synthesis measured during the next 10 min, a significant increase was not observed. A similar time-dependency has been observed with the increase in synthesis produced by increased potassium¹⁶. Whether or not this time-dependency of the increase in synthesis is related to a similar time-dependency of transmitter release has yet to be determined.

These results demonstrate that isolated synaptosomes can respond to depolarising concentrations of veratridine with a calcium-dependent increase in the rate of catecholamine synthesis. These findings show that the interact neurone is not necessary for the production of a stimulation-induced increase in neuro-transmitter synthesis, and are consistent with the suggestion that synaptosomes are capable of a depolarisation-induced transmitter release⁶. These observations may be relevant to studies of neurotransmitter synthesis not only in adrenergic, but also in serotonergic and cholinergic synaptosomes.

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Table 1 Effect of tetrodotoxin on the veratridine-induced increase in dopamine synthesis

	Dopamine synthesis (nmol h ⁻² g ⁻¹)
Controls	9.54±0.53 (12)
Tetrodotoxin	9.50±0.57 (12)
Veratridine	14.7±0.46 (12)*
Tetrodotoxin + veratridine	10.5±0.43 (12)

Aliquots of the striatal P_2 fraction were incubated for 5 min at 37°C either without further additions or in the presence of tetrodotoxin (2×10^{-7} M), followed either by the simultaneous addition of veratridine (7.5×10^{-5} M) plus L-1-¹⁴C-tyrosine (1×10^{-5} M) or by the addition of tyrosine alone, and incubated for an additional 5 min. The apparent rate of synthesis was calculated by dividing the d.p.m. of product formed per hour per gram of original tissue by the specific activity of the tyrosine added to the medium. The normal incubation medium had the following composition: NaCl, 125 mM; KCl, 5 mM; CaCl₂, 1 mM; MgCl₂, 1 mM; glucose, 10 mM; ascorbic acid, 1 mM (made fresh daily); and Tris-HCl, 50 mM pH 7.4. Values represent the mean ± s.e.m. The number of observations is in parentheses.

* $P < 0.001$ controls, $P < 0.001$ tetrodotoxin plus veratridine (t test).

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Suppression of fibrinolysin T activity fails to restore density-dependent growth inhibition to SV3T3 cells

SMALL quantities of proteolytic enzymes added to cultures can cause untransformed fibroblastic cells to manifest transiently the altered growth potential^{1,2}, enhanced lectin-mediated agglutinability³ and enhanced glucose transport⁴ characteristic of fibroblast cultures transformed by oncogenic viruses. Thus, the enhanced proteolytic activity of cells transformed by both oncogenic DNA viruses^{5,6} and RNA viruses⁷ may play an important role in the loss of density-dependent growth inhibition exhibited by virus-transformed cells. In particular, Reich *et al.* have shown that cells transformed by simian virus 40 (SV40) or Rous or murine sarcoma virus produce increased levels of a proteolytic activity (fibrinolysin T) which hydrolyses ¹²⁵I-fibrin^{8,9}. This fibrinolysin T activity is the result of the conversion of serum plasminogen to plasmin by a plasminogen activator (cell factor)^{10,11}. In addition, using plasminogen-deficient serum prepared by affinity chromatography, Reich *et al.* have demonstrated plasminogen dependence of several phenotypic parameters associated with viral transformation¹². We have used ε-aminocaproic acid (EACA), an inhibitor of plasminogen activation¹³ and fibrinolysin T activity⁸, and found that suppression of the fibrinolysin T activity of SV40-transformed 3T3 (SV3T3) cell cultures does not restore density-dependent growth inhibition to these cells. This suggests that the enhanced plasmin level in SV3T3 cell cultures is not responsible for loss of density-dependent growth inhibition in this cell line.

We added medium containing 10 mg ml⁻¹ (76.3 mM) EACA (Sigma) to Swiss SV3T3 cells after plating them on ¹²⁵I-fibrin coated dishes⁸, and simultaneously determined the effects of EACA on cell growth and release of ¹²⁵I-fibrinopeptides. The results (Fig. 1 and Table 1) show that fibrinolysin T activity was relatively low on the first and second days after plating the SV3T3 cells, but by the end of the third day in culture extensive hydrolysis of the ¹²⁵I-fibrin was apparent. (Because the cell sheet peeled off the Petri dish at cell densities greater than 12 × 10⁶ per dish, fibrinolysin T could not be assayed on untreated SV3T3 cells after day 4.) In contrast, fibrinolysin T activity in EACA-treated cultures remained low and relatively constant for at least 7 d after plating. The inhibitory effect of EACA on fibrinolysin T activity was rever-

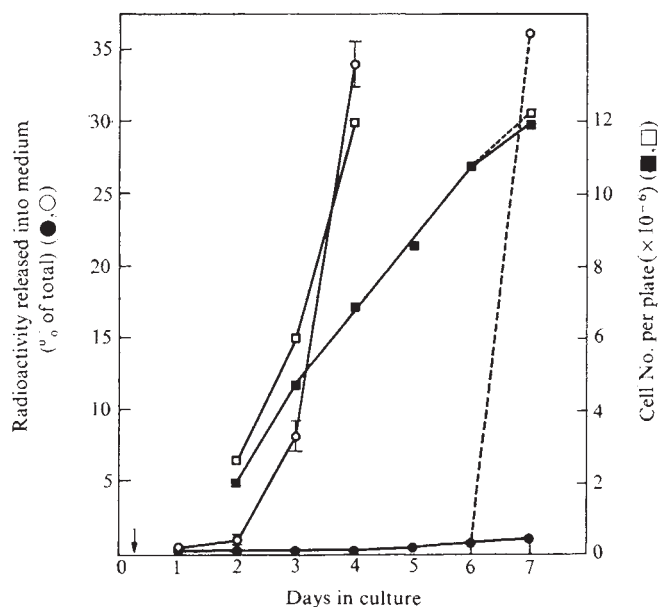


Fig. 1 Growth and fibrinolytic activity of Swiss SV3T3 cells treated with ε-aminocaproic acid. At time zero, 5 × 10⁵ Swiss SV3T3 cells in 5 ml of Dulbecco's medium + 10% foetal calf serum were seeded into 60-mm Falcon plastic Petri dishes coated with ¹²⁵I-human fibrinogen (10 μg cm⁻²; total radioactivity 1.17 × 10⁶ c.p.m. per dish) which was converted to fibrin before plating cells according to Unkeless *et al.*⁸. Five hours later, the medium was removed and 5 ml of fresh Dulbecco's medium + 10% foetal calf serum with or without 10 mg ml⁻¹ EACA was added (↓). At 24-h intervals thereafter, the cell culture medium was removed, aliquots were assayed for released ¹²⁵I-fibrinopeptides as described⁸, and replaced with 5 ml fresh medium with or without EACA has been subtracted. The activity detected represents the accumulated radioactivity during a 24-h incubation period. Each point represents the mean value (±s.d.) of the average of duplicate counts of replicate determinations on separate plates. Cell growth was determined on ¹²⁵I-fibrin-containing plates which were seeded in parallel with those used for enzyme assays. In each case the medium was changed at 24-h intervals. Cell counts were determined on trypsinized cell suspensions using a laser beam cell counter (Cytograph). Fibrinolytic activity: ○, control; ●, EACA-treated. Cell number: □, control; ■, EACA-treated. After removal of EACA, both fibrinolytic activity (●, ○) and cell number (■, □) increased during the next 24 h.

sible, since changing to medium without EACA on day 6 resulted in extensive release of ¹²⁵I-fibrinopeptides during the next 24 h (Fig. 1). Most important, under conditions where fibrinolysin T activity had been suppressed 83-98% by EACA, Swiss SV3T3 cells continued to grow and eventually reached the same cell density as the untreated control culture. Thus, essentially complete suppression of the fibrinolysin T activity of SV3T3 cell cultures failed to restore density-dependent growth inhibition to these cells.

As Fig. 2 shows, the fibrinolytic activity of untreated Swiss 3T3 cells was also relatively low for the first 2 d after plating, increased sharply on days 3 and 4, and then decreased on days 5 and 6. We have evidence from other experiments (unpublished data) that elaboration of cell factor depends on the growth state of the culture and is decreased when 3T3 cells become confluent. This may account for the diminution of fibrinolytic activity on days 5 and 6 (Fig. 2), although depletion of the ¹²⁵I-fibrin substrate may also be responsible in part. EACA (10 mg ml⁻¹) treatment of 3T3 cultures leads to 92-100% inhibition of their fibrinolysin T activity (Table 1). In addition, EACA treatment caused 3T3 cells to cease increasing in cell number about 2 d earlier than untreated cells and at a lower final cell density (EACA-treated: 8.7 × 10⁵ cells per dish; untreated: 1.5 × 10⁶

Table 1 ε-aminocaproic acid inhibition of the fibrinolytic activities of Swiss 3T3 and SV3T3 cells

Days	SV3T3			3T3		
	-EACA	+EACA	Inhibition %	-EACA	+EACA	Inhibition %
1	0.40*	0.05*	88	0.60*	0.05*	92
2	0.35	0.06	83	2.65	0.05	98
3	1.36	0.05	96	15.42	0	100
4	2.83	0.05	98	13.92	0	100
5	—	0.06	—	4.96	0	100
6	—	0.08	—	0.29	0	100
7	(2.96)†	0.10	97	(1.33)†	—	—

* Activities (% of total) without correction for cell number.

Total = 1.17 × 10⁶ c.p.m. per dish.

† Activity of cells 24 h after removal of EACA from growth medium.

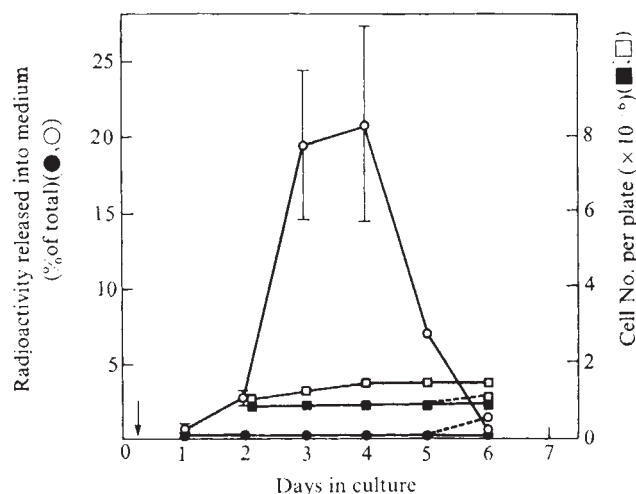


Fig. 2 Growth and fibrinolytic activity of Swiss 3T3 cells treated with ϵ -aminocaproic acid. Experimental details and symbols are as described for Fig. 1. Swiss 3T3 cells were seeded at 5×10^5 cells per dish.

cells per dish). The inhibitory effects of EACA on the final cell density and fibrinolytic activity of 3T3 cells were also partially reversed within 24 h after removal of EACA (Fig. 2).

Treatment of 3T3 and SV3T3 cells with 10 mg ml^{-1} EACA for 45–48 h inhibited incorporation (c.p.m. mg^{-1} protein) of a mixture of radioactive amino acids into acid-precipitable material by 40% and 45% respectively. Similarly, incorporation of ^3H -uridine into acid-precipitable material was inhibited 21% (SV3T3) and 15% (3T3), and incorporation of ^3H -thymidine was depressed 10% (SV3T3) and 40% (3T3). Since we have previously shown that treatment of these SV3T3 cells with low doses of cycloheximide depresses protein synthesis and leads to a dose-dependent growth inhibition¹⁴, the decreased growth rate of EACA-treated SV3T3 cells was probably a consequence of the inhibition of protein synthesis in EACA-treated cultures. Inhibition of protein synthesis by EACA may also have been responsible for reducing the final cell density of EACA-treated 3T3 cells (Fig. 2)¹⁴.

Studies on the metabolism of ^{14}C -EACA (New England Nuclear Corp.) have demonstrated (1) that EACA is taken up into a trichloroacetic acid (TCA)-extractable pool by both Swiss 3T3 and SV3T3 cells to approximately the same extent on a per cell basis and (2) that EACA is quite stable in cultures of both cell types since less than 0.2% of the input ^{14}C -EACA was broken down and reincorporated into TCA-insoluble cellular material during a 24 h incubation (R.O.R., B.Ash and P.H.B., unpublished data). The high anti-fibrinolytic activity and metabolic stability of EACA, coupled with its low cytotoxicity, thus make it a useful agent with which to probe the involvement of fibrinolysin T activity in viral transformation.

Our results demonstrate that extensive fibrinolysis takes place under normal growth conditions in cultures of both untransformed 3T3 and transformed SV3T3 cells. This is so, even though the cells were cultured in medium containing foetal calf serum, which contains relatively high levels of inhibitors of fibrinolytic activity^{8,9}. Our assay for fibrinolytic activity differs from others, however, in that it measures cumulative proteolytic hits over a prolonged period. Prolonged incubation may be required to detect low levels of fibrinolytic activity since the ^{125}I -fibrin substrate is a complex, multi-stranded, cross-linked molecule and more than one proteolytic cleavage may be required to liberate ^{125}I -fibrinopeptides into the medium.

It is also interesting that the untransformed 3T3 cell line exhibited greater fibrinolytic activity per 10^6 cells during the growing phase than did its SV3T3 counterpart (Table 1). Thus, SV40 transformation of 3T3 cells did not appear to lead to increased levels of intrinsic fibrinolytic activity in SV3T3 cells.

Removal of EACA from SV3T3 cultures, however, resulted in considerably more fibrinolytic activity per 10^6 cells than was observed when EACA was removed from 3T3 cell cultures. Thus, there appeared to be a relative reduction of fibrinolytic activity in dense cultures of 3T3, but not SV3T3 cells. The nature of this density-dependent reduction of fibrinolytic activity is under investigation.

At the concentration used in these experiments (0.076 M), EACA probably interferes with fibrinolytic activity in several ways. It can inhibit activation of plasminogen to plasmin by cell factor^{8,13}, probably by binding to and altering the conformation of plasminogen¹⁵. EACA may also interact with fibrin and thus directly inhibit the hydrolysis of fibrin by plasmin¹⁶. Finally, EACA may reduce the amount of available cell factor through its inhibition of protein synthesis. Ambrus *et al.*¹⁷, however, have reported circumstances under which EACA almost completely inhibited the fibrinolytic activity of plasmin while it failed to reduce the caseinolytic activity of similar plasmin preparations. Thus, in our experiments, although the fibrinolytic activity of the EACA-treated cultures was almost eliminated, residual plasmin activity for other substrates may have remained. We are investigating whether such residual plasmin activity exists and whether it plays a role in loss of density-dependent growth inhibition.

Our results show that essentially complete suppression of fibrinolysin T activity failed to restore density-dependent growth inhibition to SV3T3 cells. In addition, we observed high levels of fibrinolytic activity in growing cultures of both 3T3 and SV3T3 cells and only when confluent 3T3 cells were compared with growing SV3T3 cells did the SV3T3 cell cultures exhibit higher fibrinolytic activity per 10^6 cells than the 3T3 cell cultures. Thus, the enhanced fibrinolysin T activity of SV3T3 cells is unlikely to be the cause, but may rather be a consequence of unrestrained cell growth. Our results are consistent with those of Ossowski *et al.*¹², who showed that while complete expression of several phenotypic properties of transformed cells (such as growth in agar, and morphology) required the presence of a serum plasminogen fraction, SV40-transformed hamster cells grew to high cell densities in plasminogen-depleted serum.

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Activation of guanylate cyclase and intracellular cyclic GMP by fibroblast growth factor

THE induction of cell growth by animal serum in quiescent cultured fibroblasts is preceded by a sequence of regulated steps¹. These steps include stimulation of cellular transport systems¹, protein synthesis¹, ribosomal and tRNA synthesis² and eventually the induction of DNA synthesis followed by cell division^{3,4}. Two of the earliest changes observed after growth induction by serum are a transient increase in intracellular cyclic GMP⁵ (10-fold) and a decrease in cyclic AMP (two-to-threefold)^{5,6,7}. It has been suggested that cyclic GMP acts as a positive intracellular signal for cell growth since intracellular cyclic GMP concentrations showed an early transient increase upon growth induction by phytohaemagglutinin whereas no changes were observed in cyclic AMP concentrations⁸, and additions of high, non-physiological (10^{-6} to 10^{-4} M) concentrations of cyclic GMP can induce substantial increases in DNA synthesis in resting fibroblasts⁵. Recently a new polypeptide hormone, fibroblast growth factor (FGF), was isolated from bovine pituitary glands⁹. FGF in combination with the glucocorticoid, hydrocortisone, and a nonspecific carrier protein, bovine serum albumin (BSA), can completely replace exogenously added serum in bringing about all the steps leading to the initiation of DNA synthesis and cell division in some lines of BALB/c 3T3 cells¹⁰. Hydrocortisone, as it fails to initiate DNA synthesis alone in the absence of serum¹¹ is considered to potentiate the action of FGF⁹ (permissive effect).

Here we show that physiological concentrations of FGF with hydrocortisone cause the same transient increase in intracellular cyclic GMP concentrations of quiescent cultures as those caused by serum. Little or no alteration, however, is observed in cyclic AMP concentrations. Furthermore FGF specifically activates the membrane-bound guanylate cyclase, but not the adenylate cyclase system. We suggest that growth-initiating polypeptide hormones interact with a guanylate cyclase system bound to the plasma membrane, in a way similar to that of the well known interaction between polypeptide hormones and the adenylate cyclase system¹².

When FGF was added to resting BALB/c 3T3 cells maintained in the presence of serum³ the concentrations of cyclic GMP rose after 10 to 20 min by a factor of 10- to 15-fold over the value in unstimulated cultures. Thereafter the concentration rapidly declined reaching approximately twice the value in resting cultures within 1 h (Fig. 1a). Cyclic AMP concentrations showed a reduction of only 20%, much less than the two- to threefold decrease observed after addition of serum⁵. The concentrations of cyclic GMP approached those of cyclic AMP for a short time—a result similar to that obtained by adding serum to these cultures⁵ and by adding phytohaemagglutinin to human peripheral blood lymphocytes⁸. It was not possible to maintain non-degenerating cultures of BALB/c 3T3 cells with only BSA in the absence of serum, but addition of low concentrations (0.1 ng ml^{-1}) of FGF could prevent deterioration of the cultures for at least 7 d (ref. 5). Addition of

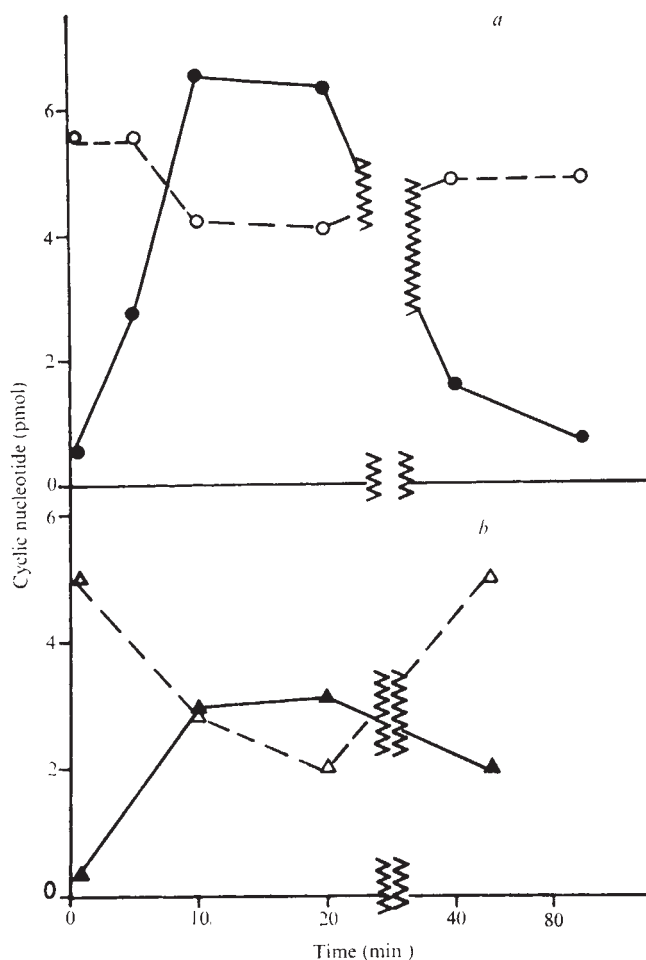


Fig. 1 Kinetics of cyclic nucleotide changes. BALB/c 3T3a cells¹¹ were grown as previously described⁵. For *a*, (FGF) cultures were allowed to become quiescent at a final cell density of 1.2×10^6 per plate before addition of 50 ng ml^{-1} FGF. For *b*, (insulin) BALB/c 3T3b cells², 6-d cell monolayers, washed with DEM, were incubated for 16 h in Dalbecco's modified Eagle's Medium containing $250 \mu\text{g ml}^{-1}$ BSA and $0.5 \mu\text{g ml}^{-1}$ hydrocortisone (final cell density as *a* before addition of $5 \mu\text{g ml}^{-1}$ insulin (bovine pancreas, Calbiochem B grade). At the times indicated 10 plates were isolated as previously described⁵ and the cyclic GMP (—●—, —▲—) and cyclic AMP (—○—, —△—) were determined by a radioimmune assay¹⁸. After centrifugation and ether extraction half the samples were digested with $3' - 5'$ cyclic nucleotide phosphodiesterase and all the samples were purified over Dowex Columns³ prior to assay. Results for digested samples (0.1 and 0.5 pmol for cyclic AMP and cyclic GMP respectively) were deducted to yield the final results expressed in pmol per 10^6 cells. Duplicate experiments agreed to within 15%. Parallel cultures radioactively labelled with ^3H -thymidine (Fig. 2) from 10 to 28 h after addition of FGF, insulin, or nothing incorporated 22, 10, or 0.6×10^5 c.p.m. into DNA, and 89%, 44% or 1.5% of the cell nuclei became labelled with radioactivity. FGF was purified from bovine pituitary glands as previously described⁹. The possibility that FGF was acting on the cells to potentiate the action of trace amounts of other growth factors adsorbed to BSA was excluded by obtaining the same results as in Fig. 2 after replacing BSA by gelatin and completely synthetic polypeptides. It was also unlikely that minor growth-promoting impurities in the insulin preparations²⁴ were responsible since similar results were obtained from commercial preparations of insulin which were further purified by column chromatography.

increasing concentrations of FGF in the presence of hydrocortisone caused concomitant increases in both the cyclic GMP concentrations measured at 20 min and the eventual induction of DNA synthesis (Fig. 2) and cell division (not shown). Virtually no changes were observed in cyclic AMP, and the small changes observed in Fig. 1 may be due to other components in serum. Resting cultures were maintained with hydrocortisone long enough for the glucocorticoid to exert

its permissive effect¹³. Omission of hydrocortisone caused a four-fold drop in both DNA synthesis and cyclic GMP concentration and hydrocortisone alone did not induce early changes in cyclic nucleotide concentrations (Fig. 2).

High, non-physiological concentrations of insulin (10^{-7} M to 10^{-6} M) can also increase DNA synthesis and cell multiplication¹⁴ after addition to quiescent fibroblasts. At these high concentrations (100 to $1,000 \times$ physiological) both the early transient increase in intracellular cyclic GMP and the depression in cyclic AMP were observed in cultures resting in the presence of serum (not shown), or in medium free of exogenously added serum with hydrocortisone (Fig. 1b). Maximal increases in DNA synthesis and in cyclic GMP concentrations were only approximately 35% to 40% of those observed for FGF in Fig. 2. The concentration dependence for the increases in cyclic GMP concentrations and for the stimulation of DNA synthesis were roughly parallel (maximal from 10^{-7} M to 10^{-6} M; not shown), perhaps suggesting a correlation. Conversely, the initial depressions in cyclic AMP occurred at much lower insulin concentrations, in the normal physiological range (10^{-10} M to 10^{-9} M; not shown). Without hydrocortisone the changes in cyclic nucleotides and the eventual stimulation of DNA synthesis were reduced two- to threefold.

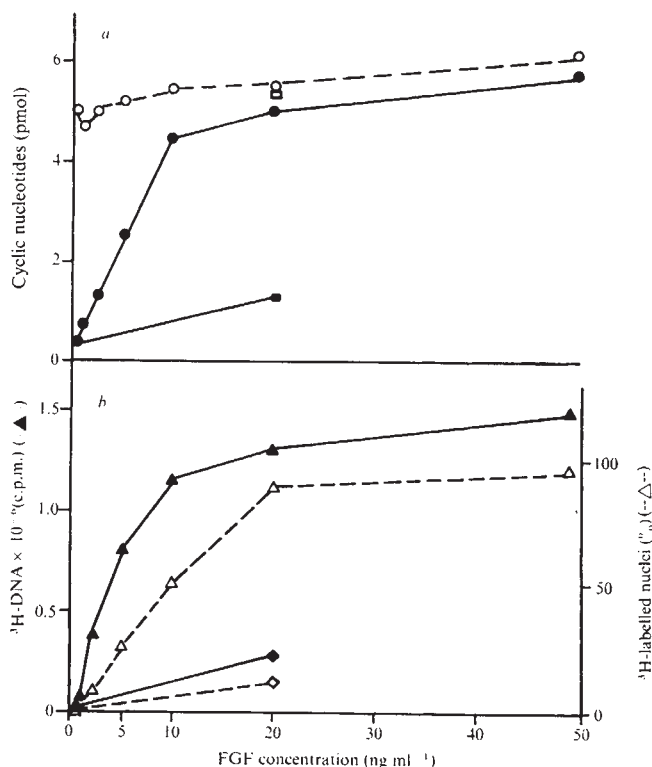


Fig. 2 Variations of cyclic GMP with FGF concentrations. Cell cultures were grown as in Fig. 1 except that 6 d after plating (confluent cultures) cell monolayers, washed with DEM containing 0.12 ng ml^{-1} FGF and $250 \text{ } \mu\text{g ml}^{-1}$ BSA, were then incubated for 2 d in this medium. Then $0.5 \text{ } \mu\text{g ml}^{-1}$ cortisol (hydrocortisone, Calbiochem) was either added (circles, triangles) or omitted (squares, lozenges). After 10 h (final cell density 1.1×10^6 per plate) varying amounts of FGF were added. *a*, Ten Petri dish cultures for each concentration were isolated 20 min later for cyclic nucleotide determinations (Fig. 1). Results are expressed in pmoles of cyclic AMP (open circles, squares) or cyclic GMP (black circles, squares) per 10^6 cells. *b*, Parallel cultures were also radioactively labelled with $3 \text{ } \mu\text{Ci ml}^{-1}$ ^3H -methyl-thymidine at $3 \text{ } \mu\text{M}$ (for DNA synthesis) or $1 \text{ } \mu\text{M}$ (for autoradiography) from 8 to 26 h after additions. The c.p.m. of ^3H -thymidine incorporated into DNA per culture (black triangles, lozenges) or the percentage of radioactively labelled cell nuclei (open triangles, lozenges) was recorded as before². Control additions of cortisol alone showed no changes in the intracellular cyclic nucleotide concentrations after 20 min or detectable increases in DNA synthesis.

Hitherto guanyl cyclase in a variety of tissues was thought to occur primarily in the membrane-free cytoplasm of the cell^{15,16}, unlike the adenylyl cyclase which is attached to the plasma membrane¹². Recently, however, a large increase in guanyl cyclase activity was obtained after treatment of particulate (membrane-containing) cell fractions with non-ionic detergents¹⁷. This finding was confirmed for 3T3 fibroblasts by the results in Table 1, where a ten-fold stimulation of guanyl cyclase activity in the particulate (microsomal) cell fraction was observed after Triton treatment, little or no increase being seen in the membrane-free cytoplasmic activity. The guanyl cyclase in the particulate fraction was also stimulated nearly three-fold by additions of FGF. No activation of the soluble cytoplasmic activity was observed, and the greatly enhanced activity in the particulate fraction after Triton treatment could not be increased by subsequent addition of FGF. Isolation of the plasma membrane fraction also confirmed these results: FGF stimulated the guanyl cyclase activity approximately sixfold whereas insulin had little or no effect (Fig. 3a).

The production of cyclic GMP during this reaction was measured by a radioimmune assay¹⁸. Even larger stimulations (eight- to tenfold) were achieved when radioactive cyclic GMP was isolated by chromatographic procedures from reaction mixtures containing $^{32}\text{P}\alpha\text{-GTP}$, at higher GTP concentrations (0.001 M) (not shown). FGF, unlike insulin^{19,20} failed however to reduce the adenylyl cyclase activity of the plasma membrane (Fig. 3b). All incubation mixtures contained $3' - 5'$ nucleotide phosphodiesterase inhibitors (theophylline and caffeine) to minimise phosphodiesterase cleavage of the newly synthesised cyclic nucleotides, as production of small quantities of one cyclic nucleotide could possibly affect rates of breakdown of the other²¹.

In a system uncoupled from other intracellular events FGF directly stimulates the guanyl but not the adenylyl cyclase of plasma membrane; presumably through a similar mechanism to that of the known hormonal stimulation of the adenylyl cyclase system¹². This is manifested in intact cells maintained in culture without added serum by a rapid, transient increase in intracellular cyclic GMP shortly after addition of FGF, little or no early changes being observed in cyclic AMP. Physiological

Table 1 Subcellular distribution of guanyl cyclase

Cell fraction	Cyclic GMP synthesised (pmol/min/mg extract)				
	Control	+ FGF	+ Triton	+ FGF	+ Triton
Supernatant	23	20	27	31	
Microsomal	9.4	27	97	108	

BALB/c 3T3a cells were grown in 10% serum as described (Fig. 1a). Cell monolayers were washed with Tris-buffered saline detached and centrifuged. This and subsequent operations were at 4°C . Cells, resuspended at 10% to 15% v/v in Buffer A (0.005 M Tris-HCl ($\text{pH } 7.4$), 0.0002 M MgSO_4 , 0.25 M sucrose) plus 0.00025 M dithiothreitol (DDT) were homogenised by douncing. The homogenate was made 0.001 M in EDTANa_2 and centrifuged at $2,000g$ for 5 min. Then the supernatant was made 0.005 M in MgCl_2 and centrifuged at $150,000g$ for 2 h. The microsomal pellet was resuspended in Buffer A + 0.00025 M DTT and stored with the microsomal-free supernatant at 4°C . Reaction mixtures (0.5 ml) contained 0.04 M HEPES ($\text{pH } 7.6$) (N-hydroxyethylpiperazine-N'-2-ethane sulphonic acid), 0.009 M MgCl_2 , 0.0001 M GTP, 0.0005 M EDTANa_2 , 0.0005 M DTT, 0.12 M sucrose, 0.01 M theophylline, 0.02 M caffeine $200 \text{ } \mu\text{g}$ of supernatant protein or $110 \text{ } \mu\text{g}$ of microsomal protein and where indicated 100 ng of FGF and 1% Triton X100. Reactions were incubated at 37°C for 15 min, terminated by boiling for 3 min, followed by centrifugation at $1,000g$ for 10 min, and the extracts stored frozen. Duplicate $20 \text{ } \mu\text{l}$ samples were assayed for cyclic nucleotides by the radioimmune assay (Fig. 1), and results are expressed as pmol cyclic GMP synthesised per min per mg protein. Blank values at zero time (5.3 and 2.7 pmol for supernatant and microsomal fractions) were deducted. The blank cyclic GMP values may be in part due to non-enzymic synthesis of cyclic GMP from GTP during the boiling step which nevertheless would be less than 2 pmol per reaction mixture, whereas non-enzymic synthesis at 37°C would be negligible²⁵. In control reactions the cyclic GMP synthesised was fully digested with $3' - 5'$ cyclic nucleotide phosphodiesterase, synthetic reactions were linear with time up to 30 min, and there was no interference of FGF or Triton at concentrations used in the radioimmune assay.

(Continued on p. 773)

British Association supplement



Architectural Review

Stirling campus • Fishlock: Science journalism • 1874 transit of Venus

Goldsmith: Popularising science • Science in Northern Ireland

Hall: Social responsibility • Murder solution by fluorescence

Cotgrove: Objections to science • Art preservation • Bullard: Rutherford's Cavendish

It has been possible in recent years to look at the British Association for the Advancement of Science from a slightly lofty viewpoint and wonder whether it is worth preserving. The annual meeting, the only occasion on which the association has surfaced, has also become a fairly regular occasion for pointed editorialising about an organisation that had outgrown its usefulness. No longer is this a reasonable line to take, and for that great credit above all to Magnus Pyke whose unique qualities have done much to breathe life into the body. If we talk here about the way ahead it is not without feeling admiration for the achievements of the recent past.

What, if anything, do scientists, those interested in science, and indeed those confronted with science need from a national organisation with a wide potential membership? Clearly not another forum for technical discussion; there are enough of these as it is, and why would a scientist take his latest results to Stirling when he could ride them to Stockholm, San Francisco or Sydney. Nor is it obvious that mere presentation and explanation of science to an enthusiastic audience will be other than an activity of moderate interest to scientists, particularly as the quality of science presentation by other media is often high.

There remains, however, a field which is as yet almost unexplored—the study of science itself. In this supplement we have tried to draw attention to some facets of science to which any scientist could contribute and from which he could draw some intellectual satisfaction. The history, socio-

logy, philosophy and way of going about science; the borderlands where science meets other disciplines; the morality of science; the way that science is presented to the public—there is much fertile ground here for regular discussion. To which we could add the deployment of scientists, science in defence, science in the Third World, education for scientists, government policy for science, nationalism in science. These are all subjects that scientists should have special knowledge of without needing to integrate a differential equation or operate a microscope. They emphasise common experiences, and may be the way towards bridging the gulf, both personal and professional, between teachers, academics, and scientists in government and industry. Here is also scope for the amateurs of science to make significant contributions to the world of learning.

The British Association is the ideal vehicle for all this, with its potentially very broadly based membership and its lack of political colour. It can point already to the increase in throughout-the-year activities both of its younger members and of its *ad hoc* committees. What is needed now is more nation-wide activity amongst its general membership and a vigorous campaign to persuade scientists that the study of science itself makes them a better practitioner. Cells of mutual instruction and discussion, rather like the Mechanics Institutes of the nineteenth century, could do the scientific community, in its broadest sense, much good and are well worth the serious attention of the association in the coming years. □

Stirling University, host to the British Association

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In this article an architect examines how the university campus at Stirling was planned. He also describes a computer study of the site carried out at the University of Strathclyde as part of a project on computer-aided design of large building complexes.

THOSE lucky enough to go to the British Association conference at Stirling this September will find one of the most beautiful campuses in Britain, sited near the citadel of Stirling Castle, the anvil on which much of Scottish history was hammered out. For Stirling is a town over which England and Scots battled for centuries, and where, in the absence of the English, the Scots fought amongst themselves. The almost unscaleable crag on which Stirling Castle stands is the gateway and key to the Highlands. Stirling had the lowest dry crossing of the Forth at the 'auld Brig' and with the resulting trade and patronage of the Scots royal house, the town grew to a prosperous centre.

The Romans under Agricola occupied the rock as a natural defence in 82 AD, legend has it that King Arthur fought the Saxons over the castle, and from 1194, in the reign of King Alexander I, the town became the 'favourite resort for the royal house'. The victorious Edward I of England pushed into Stirling in 1296, routing the locals, but Wallace replied by defeating the invaders. The English were down but not out and Edward returned; after a furious siege, they retook the castle. By 1313 the indomitable Scotsman Bruce had the castle under siege, and the following year Edward II marched to its relief but was blocked fair and square at Bannockburn where Bruce won a much hailed victory. Bruce then dismantled the castle to prevent its misuses by the dreadful English but Edward III was soon back and so the battles continued. The Scottish kings from Richard III to James VI resided with the court at Stirling. The uncertain form of the Scottish state, with its bloody tribal or clan wars, litters the royal history with assassinations, torture, plots and counter plots but, by the time of James VI, the framework of laws and Parliament were established, although the Western Isles chiefs were never cowed in the same way as the English Barony. The battle of Sheriffmuir in 1715 saw the highlanders and lowlanders fighting it out. In 1745 the castle was strongly held for the protestant crown, but catholic Prince Charles took the town in triumph. The town Stirling reflects the royal patronage with the castle and the magnificent store of buildings such as the 'Argyll Ludging' one of the finest examples of Scottish renaissance extant, built in 1630 by the Earl of Stirling.

New university

Returning to the present day, the 1950s and early 1960s saw the change of government policy towards an expansion of higher education, culminating in the long awaited Robbins report which recommended six new universities of which at least one, if not two, should be located in Scotland. The new university was to be the first for 300 years on Scottish soil, which, interestingly, boasts four ancient universities whereas England has only two.

The burgh of Stirling decided in October 1960 to do all in its power to attract the new university. Its competitors

were six other Scottish towns—Ayr, Cumbernauld, Dumfries, Falkirk, Inverness and Perth—which simultaneously entered the fray to attract the project.

The University Grants Committee (UGC) felt that it wished to found universities in medium sized towns, where people welcomed a new university, where land was cheaply available and the existing town offered prospects for the development of town-grown facilities. An investment in terms of capital, expanded job opportunities and cultural pump priming, provided by a university, would act as a regenerative force, possibly attracting specialised light industry into the bargain.

The lobbying was enthusiastic if not downright aggressive, Inverness arguing the benefits to the Highland economy, Stirling and Falkirk their nearness to the main centres of industry and population. Cumbernauld was felt to be too new, Perth to be near the university towns of Dundee and St Andrews, Dumfries and Ayr to be too isolated. The argument was really between Inverness, Falkirk and Stirling, with leanings towards the latter two.

The Falkirk-Grangemouth area is one of the most rapidly expanding in Europe, even more so with the advent of North Sea Oil. Falkirk could accommodate a university with both technical and humanities faculties and the town was large enough to offer a choice of 'digs' or rented flats. But middle class nonindustrial Stirling offered a magnificent site.

When looking at university planning in the stringent financial climate of 1974, one should not forget those heady days of the 1960s when governments jealously viewed each other's 'graduate count' as an international virility symbol. The euphoric days saw the UGC dispensing rapidly expanding resources and the choice of Stirling related to the general pattern of UGC policy. In Britain, as in many other parts of the world, university planning is as dominated by the Oxbridge ethos as vicars are by Gothic. Universities are in stone towns, in 'nice places; thus historic York, although surrounded by existing universities, gets a new

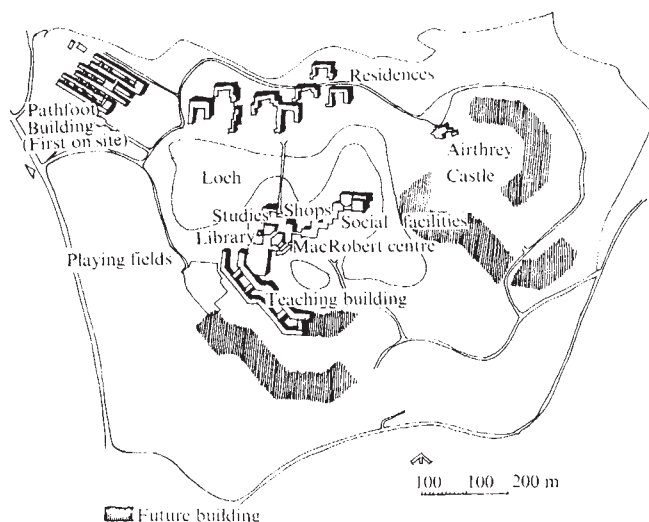


Fig. 1 Present site plan for a campus for 3,000 students.

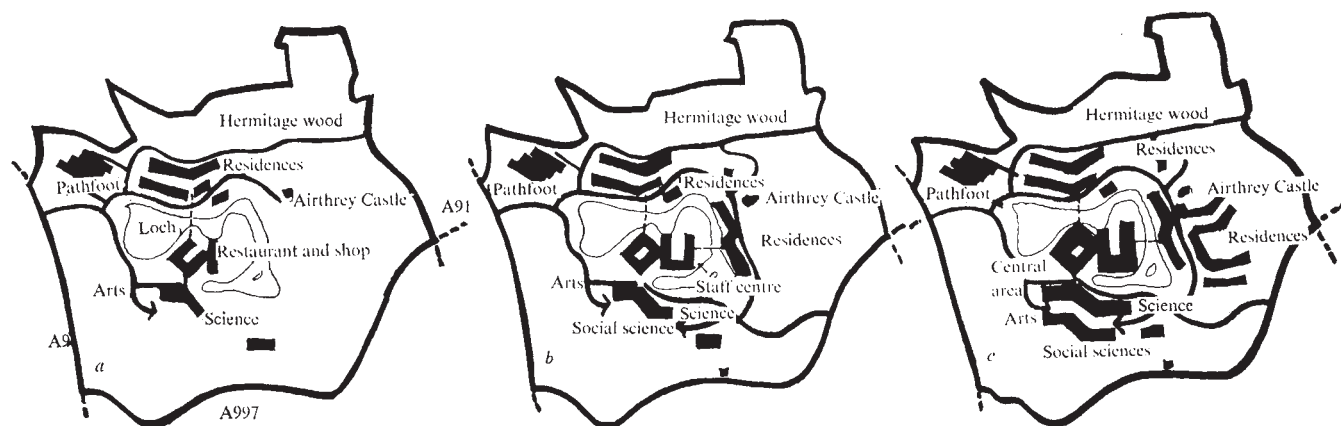


Fig. 2 a, The site in 1971; b, the site in 1974; c, possible site plan for 6,000 students.

university, whereas industrial Teesside just to the north, an industrial conurbation three times the size, does not. Almost incredibly, prosperous Bath, a mere 12 miles from the existing and famous University of Bristol, gets a new university; the town, although stone, pretty and small like Stirling, being almost incapable of supporting facilities that allow the word 'universities' to have much meaning. In their more lunatic moments, people were even suggesting Stamford, a town of 10,000 but oh! such a pretty place. The ivory tower concept dominated the pattern of thinking and in this way Stirling was selected while Scotland's fastest growing population centre was passed by.

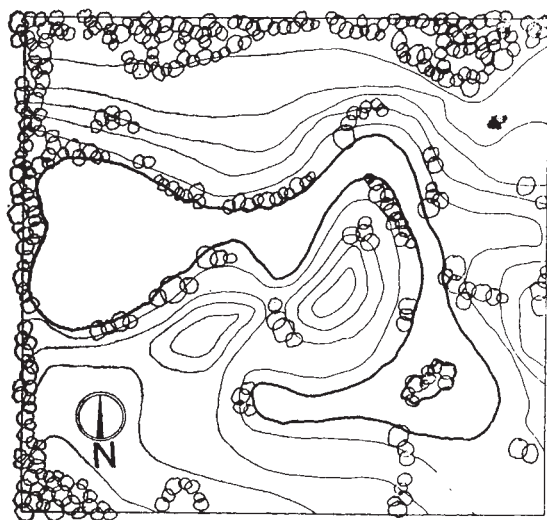


Fig. 3 An area of the site around the lake.

The decision in favour of Stirling, when announced, was rightly made final, but of course there were howls of anguish from Inverness. In Falkirk where the committee chairman, Andrew Duncan, had made getting the university his life's work, bewildered and bitter comments about 'the snob town' of Stirling were heard.

Stirling is on the new A80 from Glasgow and the M9 for Falkirk and Edinburgh, and this and the sheer magnificence of the site were major factors in its selection. The site of over 300 acres on the Airthrey Estate lies between the west slopes of the Ochills and the wooded area of Abbey Craig on which stands the splendid Wallace memorial, a flamboyant victorian bombastitude from which the view is well worth the climb. The site had an existing maternity hospital in the old castle and of course this had to be closed, the town council thus neatly securing a new university and guaranteeing the building of a new £1 million maternity hospital.

The first vice-chancellor, Tom Cottrell, was appointed in 1965 and set out the main objectives: there were to be three main areas of study, arts or humanities, basic sciences and social sciences. From the start it was intended that there would be minimal boundaries between these, thus continuing the valuable traditional assets of a general education given within the Scottish schools system. In 1967, 1968 and 1969 the university was to take 130 to 200 students, in 1971 a further 603. In 1972 the intake was 640, the intention being to have a steady 3,000–5,000 students by 1975. Although there is room on the university site for further expansion, the present budget will not allow this for the time being.

Buildings

The design and building programme was the responsibility of the architects Robert Matthews, Johnson Marshall and Partners. In 1966, the development plan was published, and has, in its essentials, been followed.

The first building, 'Pathfoot', was rapidly erected and positioned so as not to inhibit future development; it served to get the academic programme off the ground. Temporary buildings were wisely avoided as they have to be upgraded or demolished later, or more likely are still in heavy use 30 years on. Pathfoot, a simple set of parallel blocks following the contours of the site and linked by crossing corridors down the slope, is one of the least obtrusive and most successful buildings; it has won several design awards (Fig. 1).

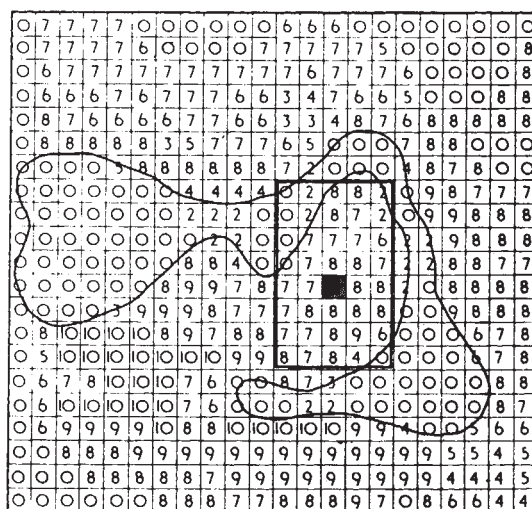


Fig. 4 Each cell has a value showing ease of building.

The architects took the artificial lake at the centre of the site as the natural focus. The main non-residential buildings to the south are the teaching, research, library and private study buildings. The object, as can be seen on development plans, is to extend southwards as student numbers grow. The level areas of the site are reserved for playing fields. The general proposed expansion can be seen in Fig. 2a, b and c. At the centre of the campus the MacRobert Centre has been built to provide an arts centre for both town and gown. The southernmost of the nonresidential buildings is the teaching block which is designed as a continuous form along the contours, expanding eastwards and southwards. A student may be involved in up to five departments within the broad based course structure and the housing of all teaching under the same roof makes mobility simple.

Although priority has always been given to the academic building programme, several coffee bars and club rooms have now been added or are under construction. The residences are built to the north of the lake and provide accommodation for two-thirds of the students. The UGC does not offer finance for residences and it is quite an achievement for the university to have raised the money by appeal and borrowing to build these blocks. The budget for the architect has obviously been very tight but the spartan interior has merit and is quite adequate. The rooms are arranged in flats or in halls of residence, the flats being generally the more popular though the halls give more seclusion for those wishing to work.

Computer study

The plan for Stirling University by Robert Matthews has made a great deal of the site. The consistency of the external cladding materials (some students say monotony) does not detract from the natural beauty of the setting. As a result of interest in university planning, a computer-aided study of the best development strategy for Stirling University was carried out at the University of Strathclyde. It was suggested that both the residential and teaching blocks should be south of the lake initially and the northern areas developed later. In addition, it was contended that with a compact development the site could accommodate a university of 12,000 students with all necessary facilities excepting some sports fields. The study attempted to develop a computer-aided design tool to assist in the laying out of large complexes of buildings. For illustrative purposes an area of the site was taken around the lake (Fig. 3).

To develop a layout plan or zoning for functions on this



The University of Stirling. With the lake as a centrepiece the site is an unusual one for a University.

site the strength of the relationships between different functions of the university was expressed on a scale from 1 to 10, a relationship of 10 being the essential need for immediate contact. Thus each department of the community, such as administration, arts, chemistry, was assigned a number describing how strongly it was connected with each of the others.

In addition, to allow for the difficulties of building on the site, a grid was drawn on the plan (Fig. 4) and in each square a number was assigned which reflected how 'buildable' that part of the site was. Plainly the lake has zeros whereas the areas to the south with gentle slopes and good foundation conditions are easily and cheaply built on and score highly.

In this way a numerical picture of what the site was like and how the university functions were interrelated could be presented to the computer. In principle, the function, faculty or department needing to have access to all others is placed on the site by choice of the designer and the others are located after this by a simple computer algorithm, to minimise the dislocation expressed in the need for proximity on the 1 to 10 scale. Rather than an actual building layout, the result is a series of zones on the plan indicating in which area a new building should be located from the point of view of easy communication and planning efficiency (Fig. 5). Various experimental computer routines were developed for three-dimensional zones and graphic outputs. The study, although simple, does provide another point of view and certainly the suggestion of a compact development, leaving larger areas of the site unspoilt, would have produced a completely different character on campus: whether it would have been better is a matter for argument.

Relationships

The University of Stirling, like any other new institution in a town, needs time to get to know its environment and to win over the town people. Its position on an isolated campus, without any substantial residence in the town, does not help. Certainly the MacRobert Theatre has been used by local dramatic societies and visiting theatre companies to the benefit of Stirling and the whole region but, as yet, there seems little use by the town of the university sports facilities; recently the university refused to go part way with the town on financing a joint swimming pool, preferring to build a small one of its own while the town built another.

It was hoped that the new employment brought by the university would encourage industry but this has not, as yet, occurred. Of course the university now employs over

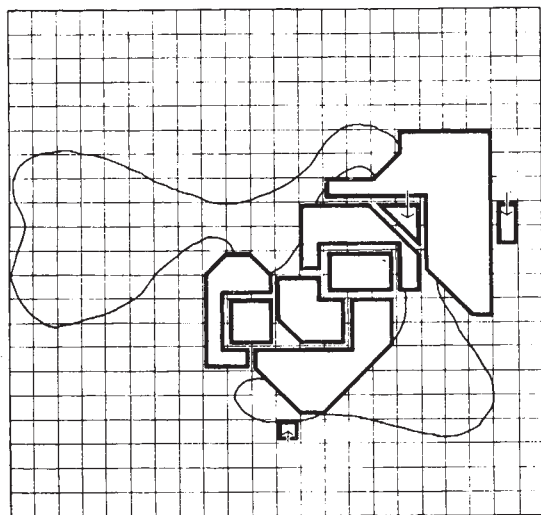


Fig. 5 The zones for a student population of 3,000.

1,000 people, which is in itself a boon; yet conversely, while more clerical and other jobs have been created so the number of people coming to Stirling expecting to find such work has increased and the availability of jobs for the local people does not seem to have markedly improved. Perhaps the most difficult point with a separate campus is the provision of all facilities on the spot—bookshops, banks and supermarkets. This is a great pity, for surely a university bookshop located in the town would provide an invaluable specialist service a small population cannot support. Perhaps if residences can be built in town in future these things may come about. A good example of how a university can generate new shops can be seen in the streets around the University of Glasgow.

The University of Stirling and the town should start thinking now about the effect of future growth of the campus; after all, a student population of 6,000 would give the campus a daytime population of about 1,000, which in a town of 28,000 will have a significant impact. The road programme and problems of general access may well have to be reassessed, as well as a monumental parking problem.

The university authorities, students and architects have done well to achieve a rapid build-up to the present almost complete campus. This has been done despite problems both logistic and academic. The courses offered are already diverse and include MSc and PhD courses in the pioneering aquatic pathology department, a unique educational degree that combines supervised experience with academic study allowing students to teach immediately on qualifying, and an Institute of Finance and Investment which offers one-year courses.

Stirling University, famous for its student outbursts in the past, now gives the impression of consciously trying to achieve a real community spirit while determined to develop a town-gown understanding. There is undoubtedly an underlying pride and mutual confidence developing between the town of Stirling and its university.

¹ Willoughby, T., Paterson, W., and Drummond, G., *Architects' Journal* (March 25, 1970).

² Matthews, R., *University of Stirling Development Plan 1960* (Johnson-Marshall and Partners, 1960).

³ *Architects' Journal* (June 20, 1973).

⁴ *University of Stirling Prospectus 1975-76*.

What makes a good science writer?

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SOME years ago a friend of mine mentioned to another research scientist that he intended to become a science writer. His colleague commented drily that it meant he would need to know ten times as much as he ever wrote on any aspect of science. That advice sometimes comes to mind when I am writing against a daily newspaper deadline in the late afternoon or early evening, aware that I am stretching my own knowledge of the subject to the limit, with no time to seek further advice. More often, however, I recall it when I am reading reports of other science writers who, whether for lack of knowledge or because their own prejudices have insulated them from the other side of the story, reveal all too plainly that their writing has out-distanced their knowledge.

Accuracy and indignation

The professional scientist's constant complaint against science writers is that they get it wrong; that they imbue with all the authority of Science some observation, opinion or conclusion which at best is open to argument and at worst is factually incorrect or misleading. It is a grievance I hear in many laboratories I visit, as well as in Whitehall and corporate headquarters. It is one of which I was made very firmly aware soon after I joined the *Financial Times* in 1967. A scientist who has since risen to become one of the government corps of scientific advisors told me bluntly that he didn't waste time reading newspaper reporting of science.

More recently the indifference this physicist then showed has changed into a genuine concern at the top of the profession for the damage that misunderstandings, inaccurate reporting and biased comment can do when published by newspapers under the authoritative sounding by-line "Our Science Correspondent". Examples range from an interruption, on wholly spurious grounds, to efforts to clean up

the oil leaking from the Torrey Canyon, to fears unnecessarily aroused by hypothetical representations of the 'hazards' of pesticides, herbicides, drugs, toiletries, nuclear reactors and nuclear by-products, supersonic airliners, and many other products of applied science. Reports that readers might reasonably expect to be written from a standpoint of some knowledge and expertise are all-too-often characterised largely by indignation and prejudice.

Indignation has tended to be the keynote of far too much science writing in the past few years. When, in the second half of the 1960s, it dawned on the public that science and technology did not have pat solutions to man's social ills and if exploited too greedily might even exacerbate them, many science writers joined enthusiastically in the assault on scientists' motives. They competed for space in some journals to the point where it was hard to distinguish their writing from that of a new breed of specialists which emerged at that time, called Environment Correspondents, created by many newspapers to provide 'gloom and doom' stories forecasting the imminence of mankind's destruction. For editors it was a fresh angle on the insatiable public thirst for bad news.

Also deeply infected by indignation at this time was the weekly journal *New Scientist*. Soon after it started in 1956 its founder-editor Percy Cudlipp, who had been one of the most eminent of Fleet Street editors, wrote that his journal was to be a

"link between science and industry. It would report technological innovations and promising lines of research. It would pay careful attention to the scientifically progressive sections of industry and would help, by describing their activities, to create a growing interest in scientific applications among industry as a whole."

In the early years its highly authoritative explanations of every facet of technology and science, written wherever possible by the foremost practitioners in a particular field, yet painstakingly edited—when necessary—for assimilation by the inexpert, were eagerly seized upon by other writers as well as by scientists anxious to keep abreast of progress

in science, if only to see that their interests were not being neglected in the goldrush.

Lest I leave the impression that early *New Scientist* editors hung on to every word, each prediction of the wise men of science and engineering, let me hasten to say that by the start of the 1960s the journal was making its own critical appraisals of projects and plans. Increasingly it was finding flaws in the proposals for harnessing science. In short it was attempting—sometimes with conspicuous success, as in the case of an ill-conceived scheme for large cross-Channel hovercraft-ferries¹—what later became dignified as the new discipline of 'technology assessment'.

Influence

The *New Scientist* has had an important influence on science writing in Britain, and probably elsewhere too. Although I do not think it has bridged the gap between the 'two cultures'—by this I mean that few people who are not professionally concerned with science trouble to read the journal—it has bridged many narrower gaps between the scientists themselves. It has also been invaluable to science correspondents on other journals, as the first stage of breaking down a complex piece of research or 'emerging opportunity' into a simple but lucid newspaper story.

Unfortunately, the influence of *New Scientist* began to wane sharply in the late 1960s. The downturn coincided with a change of publisher, from a small but dedicated company to a large and remote empire. It also coincided with two changes of editor, both of whom interpreted their role not as helping scientists to adapt to the changing attitudes of society towards science and technology, but as lending their weight to the attack. What characterised many of its editorial assaults at this time was not the cool, dispassionate and knowledgeable writing which distinguished so many of its early articles and leaders in the first decade of the journal's life, but the irrational, emotion-laden tirade of the writer who is composing for effect and not going to allow himself to be deflected or confused by facts.

A low threshold of indignation is the *sine qua non* for the successful investigative reporter, of the kind that exposed the Watergate debacle in the *Washington Post*, for example. But as the two Pulitzer prize-winning reporters in this case make so plain in their book *All the President's men*² they also exercise uncommon care in sifting and double-checking their facts and deductions before publication. (The rigorosity of this process may owe much to the fact that Howard Simons, their managing editor, who launched the paper's investigations into Watergate, was for many years its highly respected science correspondent.)

Too many science correspondents in the last few years have assumed that a low threshold in indignation and an input of information from someone, somewhere in science, however obscure, was enough to add up to a story. Too many have been ready to select facts and sources regardless of their intrinsic merit and to overlook a much greater weight of contrary evidence. Too many, in short, have flouted the basic principles of the profession they are being paid to write about, in quest of a story to meet the supposed public taste for gloom and doom.

A science writer who accepted without question claims for perpetual motion would be laughed out of court. But no less improbable assertions are often implied about the explosibility of nuclear reactors, the hazards from radioactivity or the damage left in the wake of supersonic transports. The referee system of exposing a man's observations and conclusions to the scrutiny of his peers, who then approve or reject them for publication in an accredited journal, is the science writer's best safeguard against the dubious claim. It may not be perfect but it is much healthier than the activities of those scientists who have tried—sometimes with devastating success—to bypass the

journals and appeal directly to a general public in no way equipped to assess the merits of their claims.

Wit and grace

Scientists, understandably, have been at a loss to know how to respond to assaults from science writers. As that formidable United States physicist, the late Dr Edward Condon, once said ruefully, when assailed by a Congressman for allegedly being a security risk, "If you say I've got a wart on my nose, I can deny it. But if you just say I'm one of the ugliest men in town, all I can do is argue that I'm really quite pretty"³. Aggrieved scientists and technologists, attacked for the 'ugliness' of their discoveries, projects and propositions, sometimes turn for help to a science writer who may lend a more sympathetic ear. It is unfortunate but the impact of a dispassionate appraisal can rarely counterbalance the damage done by the preceding highly dramatised story. One instance where the counter-attack was very successful, however, came after lurid newspaper accounts of the mercury found in fish landed in Britain, when the science correspondent of *The Observer* reported that fish from the Smithsonian Museum, caught in the 1920s, had been shown to contain at least as much mercury when assayed by the same method.

The one real source of redress a scientist has who feels the facts have been ignored or distorted—and I can assure readers that it can be a very effective form of redress—is a brief letter to the Editor. Few newspaper editors will ignore a letter from, say, a professor or research director who says bluntly "your science correspondent was wrong". Fewer still will decline to publish it prominently if the letter puts the facts straight with some leavening of wit or grace.

If I have a general literary complaint about science writing and the reporting of science, technology and medicine, it is that so much of it is so humourless, so lacking in wit and charm. Nowhere is this more evident than in the stories that reek of indignation. Yet science itself is not at all like that. Names that come easily to mind of scientists who can be very witty about the failings and faults of their own profession include Victor Rothschild (as in his 1971 Royal Society of Arts lecture on the need for reorganisation of government science in Britain), Kenneth Mellanby and Magnus Pyke. Most recently, in the pages of *Nature*, we have the splendid example of Erwin Chargaff with a delightfully ironic essay, criticising the validity of much present-day biology and the honesty of such euphemistic evasions as "the results that I reported last year are based on facts that are no longer available"⁴.

Far too often the facts science writers reported last year are 'no longer available', either. Sometimes, inevitably, this is unavoidable, and no fault of the writer, who is simply reporting results, conclusions or claims, formally or publicly stated, that are later overtaken or invalidated by more research or other events. Sometimes it is the result of injudicious selection of 'facts', as was the case in a protracted (but quite unsuccessful) assault on a well known domestic pesticide by a journalist who, when I challenged his motives, simply said "Well, what's wrong with flies?" Sometimes, unfortunately, it is the result of misunderstanding, misinterpretation, or simply miscalculation—as when a prominent story in *The Guardian* of alleged pollution of the English Channel turned out to be based on calculations assuming that the channel had but two dimensions⁵.

Lessons

Seven years of reporting and appraising science, technology and medicine for the *Financial Times* has taught me some harsh lessons about the scope and limitations of newspaper reporting of science, and the pitfalls of taking too freely the word of its practitioners. A background which

includes experience of industrial science and of reporting industrial practice has encouraged, I think, more sympathy for the formidable difficulties of translating the discoveries of science into practice, often dismissed impatiently by science writers as mere parsimony or 'engineering detail'.

But it has also taught that the scope is much greater than the limitations; that given editors with a genuine interest and curiosity about science—its discoveries and opportunities and the people who make them and who take the decisions—the scope is immense. The *Financial Times* enjoys such editors, and has done so certainly since the post-war years when the late Professor Sir Francis Simon, head of the Clarendon Laboratory, Oxford, was also its science correspondent. It is a paper of industry and commerce, specialising in facts and fair interpretation and not dependent for sales on polemics, propaganda or unabashed entertainment.

As Science Editor I am one of about a score of specialised feature writers, mainly writing regular articles of up to 2,000 words—much longer than most newspapers normally accept—sometimes at the Editor's instigation but most of the time as a result of my own quarrying among the papers or people of science. In the past twelve months, for example, it has published over 70 feature-length articles under the by-line of its Science Editor, and many more on such technologies as aerospace and computers by other staff feature writers.

What I cannot claim is that those articles represent a complete spread of science and technology. The reader will find little on astronomy, genetics or sex-change surgery, for example. But he will find a more complete (and I would venture more accurate) coverage of the science, technology and politics of nuclear energy than any other newspaper has carried. He will also find many articles discussing the organisation, management and funding of science, rare indeed outside the pages of specialised journals on research management.

No two national newspapers in Britain produce a similar science coverage. You can take your pick from a wide variety of interests and levels of treatment, of preferences and prejudices. At its best the reporting of science compares favourably with that of such countries as the United States, West Germany or Sweden.

It has recently been proposed quite seriously to me that science correspondents should exercise as much responsibility as the referees of scientific papers. In principle, I agree and would like to see the suggestion developed more fully; but in practice I cannot imagine how such standards could be enforced, when science correspondents must work constantly under constraints called deadlines that no referee would tolerate.

What I think scientists are entitled to ask of those who write regularly about them is that they will exercise the basic tenets of the scientific approach; that they will reject illogical argument, that they will reject stories where the facts do not fit, that they will not suppress facts that conflict with their arguments. Newspapers nowadays employ very bright people as journalists, many of them university graduates. Most of them are perfectly capable of handling in an interesting and accurate way most of the science stories that come to light. If the science correspondent has any claim at all to distinction as a specialist writer it is surely that he is versed in the scientific method—the way scientists approach a situation—and thus better equipped to spot the fallacies for his readers.

¹ Fishlock, D., *New Scientist*, 590–591 (March 5, 1964).

² Bernstein, C., and Woodward, B., *All the President's men* (Simon and Schuster, New York, 1974).

³ Branscomb, L. M., *Physics Today*, 27, 68 (June, 1974).

⁴ Chargaff, E., *Nature*, 248, 776 (1974).

⁵ Lord Zuckerman, *Times Literary Supplement*, 1419–1422 (November 12, 1971).

The transit of Venus in 1874

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Observations of the 1874 transit of Venus seem to have been based on a misguided belief that nineteenth century techniques were superior to those of the previous century. Here A. J. Meadows explains, with the benefit of hindsight, how the expectations of the nineteenth century astronomers were not fulfilled.

THE average distance from the Earth to the Sun is a fundamental astronomical constant: it forms the basis of the scale of distance used both outside and within the Solar System. Outside the Solar System, the Earth–Sun distance acts as the base line for the measurement of the distances of nearby stars, and so, ultimately, of the entire Universe. Within the Solar System, any single estimate of distance can be used to calibrate all remaining distances by using Kepler's third law. For example, if we know the Earth–Sun distance we can work out the Venus–Sun distance:

equally, however, we can derive the Earth–Sun distance from a knowledge of the Earth–Venus distance at any instant.

The classical method for the determination of distance in astronomy has always been by the use of parallax. This requires three things: a relatively nearby object, a distant background, and two observers at either end of as long a base line as possible. When the observers measure the position of the object relative to the background, it does not seem to be in exactly the same place for both. The difference—the parallax shift—decreases with the distance of the object; so the parallax provides a direct measure of the object's distance. The current value of the solar parallax is 8.794", although in fact, it is known to much better accuracy. Thus, two observers situated at the ends of an equatorial radius of the Earth would see the Sun displaced against the background stars by that amount. Clearly, the direct detection from Earth of so small a displacement of the Sun is virtually impossible. The prob-

lem of determining the solar parallax has, therefore, been one of finding a closer and easier object to measure than the Sun.

Observing Venus to determine parallax

Of all the planets, Venus comes closest to the Earth: its minimum distance from the Earth at conjunction is, on average, only half that of Mars. Unfortunately, the value of parallax measurements for Venus is diminished by its juxtaposition to the Sun when at conjunction, which makes accurate visual observation extremely difficult. The way out of this impasse was suggested by Edmond Halley in 1716. Venus usually passes above, or below, the Sun as seen from the Earth; but on rare occasions, because of the mutual inclination of the orbits of both planets, they are so placed that observers on Earth actually see Venus transiting the solar disc. Under these circumstances, the brightness of the Sun becomes an advantage, rather than a disadvantage, for Venus appears as an obvious and easily measurable, black dot on the Sun's surface. Halley proposed that, during a transit, Venus should be observed from several widely spaced stations on Earth. Observers at points distant from each other would see the planet describe slightly different paths across the solar disc. Therefore, the duration of a transit would depend on the observer's position. Measurements of the times of the beginning and end of the transit could therefore be converted into a value for the parallax of Venus at conjunction and, thus, into a figure for the solar parallax.

At the time the main problem with Halley's proposals was the infrequent occurrence of transits of Venus. At present, the transits occur in pairs separated by a gap of 8 years, but with a delay of over a century between successive pairs. In Halley's time, the next pair were not due until 1761 and 1769: but, to eighteenth-century astronomers, the wait seemed worthwhile, for the method apparently provided much greater accuracy than any other then available. (From his observations of a transit of Mercury in 1677, Halley estimated that a transit of Venus should provide a value for the solar parallax which would be accurate to one part in six hundred—far better than other eighteenth century methods.)

Great preparations were made for the transit in 1761, with expeditions dispatched to distant parts of the world'. But the results were a major disappointment: the extreme values obtained for the solar parallax differed by as much as 20%. It was generally agreed that the main inaccuracy had been introduced by an unexpected 'black drop' effect

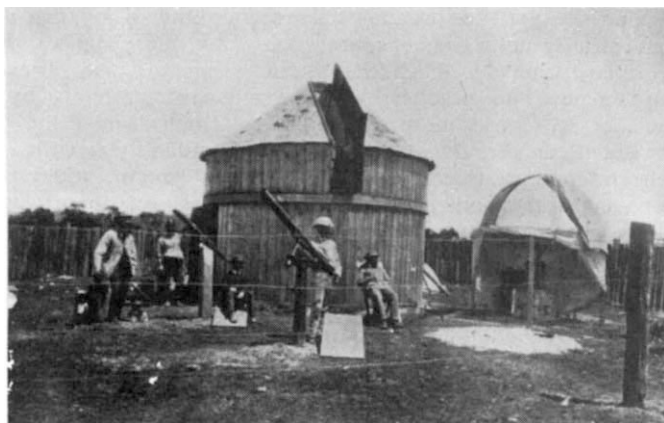


Fig. 2 Observers waiting for the transit to begin.

as Venus encroached on to the solar disk. (As the limbs of Venus and the Sun approached they seemed to flow together—an effect that made accurate timing of the beginning and end of the transit very difficult.) Forewarned, the observers at the following transit, in 1769, obtained rather better agreement; but their results were not properly reduced until the 1820s, when the work was undertaken by the German astronomer, Encke. The final figure he obtained for the solar parallax was $8.571''$, a value that was widely accepted for a quarter of a century. By the latter part of the 1850s, however, it became evident that this made the Earth too far away from the Sun. Solar gravitation acts differentially on the Earth-Moon system because the Moon is sometimes closer to the Sun than is the Earth, whereas at other times it is more distant. As a result, the motion of the Moon is dependent on a factor that involves the mean distance of the Sun. By the mid 1850s lunar theory had become sufficiently refined to show that Encke's result could not satisfy the observational data on lunar motion. It therefore became essential to re-determine the solar parallax.

A different approach

In 1857, G. B. Airy, the Astronomer Royal, proposed that arrangements should be made for detailed observations of the next transit of Venus, due on December 9, 1874, to obtain a better value for the solar parallax. Airy was confident that the technical advances since the eighteenth century would permit a much more accurate result to be obtained. His colleagues agreed with him, and he was put in charge of a major British campaign (to be linked ultimately with similar campaigns mounted by a number of other countries).

One of Airy's first decisions was to abandon the use of Halley's method of observation, and to substitute instead one proposed by the eighteenth century French astronomer, Delisle. Halley's method, which involved timing both the beginning and the end of the transit, required that the entire transit should be visible from each observing station. This meant that any change in weather during the course of the transit could vitiate the result. More importantly, it meant that large areas of the Earth's surface, from which only the ingress or the egress could be seen, were ruled out as places for observation. Delisle's method, on the other hand, only required the timing of one contact—either ingress, or egress. To compensate for this, it required—in contrast to Halley's method—a very precise determination of the longitude of the observing station. Which approach was preferable depended on the particular circumstances of the transit; Airy's analysis of the 1874 transit suggested that Delisle's method would be more suitable. He therefore began to search for a series of

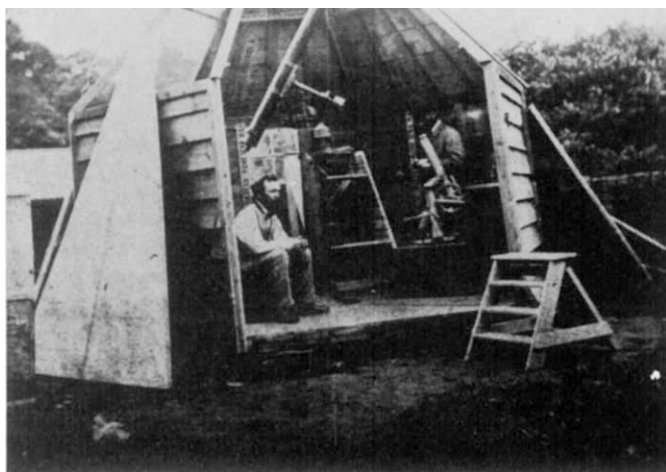


Fig. 1 One of the huts erected at Greenwich for testing prior to observations of the transit of Venus in 1874.

widely spaced stations from which that type of observation of the transit could be made. As the zone of visibility for the 1874 transit was centred on the Pacific, suitable sites necessarily tended to be situated on islands. That forced Airy into extensive consultations with the Hydrographer for the Navy, Admiral Richards; for the charting of Pacific islands still left something to be desired at that time.

Airy outlined his proposals for observations of the transit at a meeting of the Royal Astronomical Society in 1868. In the following year, another prominent member of the Society, R. A. Proctor, attacked Airy's conclusions, claiming, in particular, that Halley's method might well be applied to the 1874 transit, and proposing that a somewhat different set of stations should be selected with that possibility in mind. Airy took no notice, but pushed ahead with his own plans, and during 1869 he obtained a sum of £10,500 from the Treasury to finance them. In 1873, however, Proctor (who had meanwhile become Secretary of the Royal Astronomical Society) once again took up the argument. This time it was pursued before the general public, especially through the columns of *The Times*. At first, Airy resisted any change in the arrangements, but eventually he agreed that additional stations should be sought. This, if anything, only served to enhance the dispute, for Proctor and his friends now entered on a debate with Admiral Richards to discuss which new stations might be occupied. Richards, in exasperation, finally observed²:

"Enthusiasts no doubt there are who, however accomplished they may be as astronomers, are wanting and cannot but be deficient on many subjects which it is as necessary to take into account as astronomy in a question of this kind; and hence we are told to send to the Antarctic Continent and to visit a variety of small rocky islets interspersed over the Southern Ocean at distances from each other varying from 1,000 to nearly 4,000 miles, many of which are actual myths, while on those which do exist it is certain that there is no anchorage for a ship, and that even landing would be generally impossible."

Proctor was not prepared to let Richards have the last word. In a subsequent supplementary issue of the

*Monthly Notices of the Royal Astronomical Society*³ he produced a chart of possible observing stations, together with the annotation:

"The chart requires no explanation beyond perhaps the remark that the islands in the less-known regions have been taken from ordinary atlases (after comparison of several), in preference to the Admiralty charts; because . . . one naturally feels doubtful about Admiralty statements which would appear to be variable according to official requirements. It did not seem well to insert any island, or group of islands, in the chart with some such note as 'Here, if convenient to those in authority, there is an island,' or 'this group of islands can be regarded as a reality or a myth as may be required,' and so on."

There, however, he had overstepped the mark; for, as Editor of the Journal at that time, he published without reference to other members of the Society. When Richards complained to the RAS Council, the result was virtually inevitable: by the end of 1873, Proctor had resigned as Secretary, and the controversy over the transit died down.

Airy had begun preparations for the transit on the assumption that the actual times of contacts would be determined visually in much the same manner as in the eighteenth century, although with better instrumentation. It was soon pressed on him, however, that the rapidly developing art of astronomical photography should also be used along with the visual method. Initially Airy was dubious, but was eventually persuaded, more especially because De la Rue, the leading British exponent of astronomical photography, agreed to take charge of preparing the photographic instrumentation. Airy therefore obtained a further £5,000 from the Treasury for this type of work, and British expeditions observing the transit carried out a mixture of visual and photographic measurements.

The raw data from the expeditions was collected together at the Royal Observatory, Greenwich, and Captain Tupman, an army officer, was put in general charge of the reductions. The work dragged on slowly until, finally, Parliamentary pressure began to build up for immediate publication: the expenditure on the 1874 transit made it, after all, one of the most expensive single scientific investigations supported by the state up to that time. When, partly as a result of the pressure, preliminary conclusions were published in 1877, the difficulty facing Tupman and Airy became apparent. The new measures of the solar parallax were no more accordant than the eighteenth century measures had been. Airy, himself, derived a final value for the solar parallax of 876"; but this represented an average from values for ingress and egress that differed by 0.11". Moreover, Stone, HM Astronomer at the Cape, obtained, from the same data a value of 8.88". The photographic results were even worse. From these, Tupman obtained a solar parallax of only 8.08"; and an independent re-examination of the material only improved this to 8.17". Part of the problem was that the type of photographic instrumentation used by most British parties was not particularly suitable for transit measurements. But even American measurements, which were better arranged, did not achieve the expected results⁴. Indeed, the deficiencies apparent in the British observations, both visual and photographic, were to varying degrees, found in the results obtained by all the participating countries.

Looking back, the observations of the 1874 transit seem to have stemmed from a misplaced belief in the superiority of nineteenth century methods and instrumentation over those of the eighteenth century. Certainly, the 1874 transit, together with the much less enthusiastically observed transit of 1882, finally delivered the quietus to this form of solar parallax measurement. Nobody will consider it worth observing the next transit of Venus, in 2004, for this purpose. Yet the idea that the solar parallax can best be

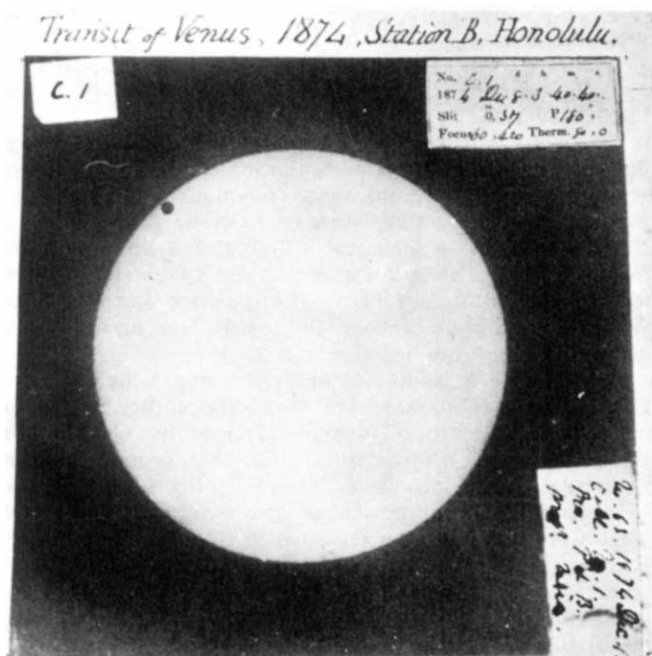


Fig. 3 Photoheliograph observation of Venus near the solar limb.

determined by observation of Venus at inferior conjunction remains valid. The present standard method involves radar observations of Venus near this point in its orbit.

All the photographs used in this article are from the Royal Observatory archives, and have been made available by Lt.-Cdr. H. D. Howse (National Maritime Museum).

¹ Woolf, H., *The Transits of Venus* (Princeton University Press, Princeton, 1959).

² *History of the Royal Astronomical Society*, 183 (Royal Astronomical Society, London, 1923).

³ *Ibid.*

⁴ Newcomb, S., *Popular Astronomy*, 2nd ed., 183–192 (Macmillan, London, 1883).

'Popularisation' of science

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With the increasing dependence of the civilised world on science, the need is not so much for 'popularisation' as for understanding and critical appreciation of scientific advances if alienation from science is to be avoided.

ASTRAY one evening recently in an unfrequented cupboard at home, I came across a copy of that pioneer publication *Penguin Science News*: to be exact, issue number four, dated July 1947. And as I turned the pages to renew with delight this old acquaintance, the editor once again spoke to me—but with words of such innocence that I was obliged to shut him up. From this surprise reunion I came away with an embarrassed feeling of sophisticated guilt, not so much in disturbing the innocent but in realising that his simple views were still held so widely. Although techniques of communication of scientific ideas to the public have developed greatly in these past three decades the philosophy of the communicators has not.

In an editorial the editor claimed that "every scientific subject, without exception, can be made clear to the layman." He added, "All the ideas of science are basically simple and understandable by the average brain," and went on, "Provided an author really understands his subject himself and has enough space to write his expanded discussion in simple words, there is nothing under the sun which he cannot clarify and teach."

In those pioneer days of science writing, I too, had such innocent views. We did not understand then, and I am not sure that many of us have grasped even today, that communication means not only to send out messages but also to receive messages from the world about us. We were concerned then only with the communicator. We assumed that if he wrote simply and well—"Goldsmith," one famous editor said to me, "you must learn to write more compellingly, otherwise your readers will ignore you—and so shall I!"—we would be read and understood. O, blessed paradisaical innocence! The final awakening came for me about 1950. I was puzzled because since 1945 we had exuded millions upon millions of words, written and spoken, on the nature of the atom, and I found that most people remained unhappily ignorant on this subject.

We were most successful in scaring them, however, so that fear and prejudice are impeding progress in, for example, the development of nuclear power plants. It is not sufficient to write clearly and well. Literate writing helps but it carries in itself no guarantee that understanding or even reading will follow. Although, I agree it helps.

This is in great part due to the primitive view of the popularisation of science which inspires so much of our thinking. It is as constricting to us as was the veneration of the circle to Galileo. He was neutral about Kepler's thesis that the planets moved in elliptical orbits because he

could not accept as significant any speculation which neglected the axiom that the circle is the perfect curved form. We are in bondage to a concept that I believe has been an important factor in alienating people from science. We have tended to use the term "popularisation of science" loosely to describe what we hope for rather than what actually happens. This is more than an exercise in semantics, for what we are concerned with is the definition of the social phenomenon which has blinded us into believing that we were enlightening the masses when the opposite was more true.

I believe it would be generally accepted that the popularisation of science is designed to make science popular (by which I mean intelligible) among non-scientists. The argument is that science is difficult to understand and that it requires to be translated into terms simple enough for the non-scientist to understand. This view has been expressed almost from the beginning of science itself.

But a certain knowledge of science spread among the public long before that. There have always been scholars and non-scholars, therefore always the need to interpret. We are aware that there was a weakness for the encyclopedic in the literature of the Middle Ages. The general cosmological system of Dante's *Divine Comedy* was based on Aristotelian, Ptolemaic and Christian ideas. The most widely read of mediaeval romances, the *Roman de la Rose* of 1270, contained statements on topics such as philosophy, medicine, physics, astronomy and theology.

In this way, general ideas about nature of the universe, the planetary system and the nature of matter were put into circulation.

The word 'science' began to enter the English language during the Middle Ages (the beginning of the 17th century.) It came from France, and was synonymous with knowledge. But the early Latin translators of Aristotle gave the adjective "scientificus" a technical meaning, and this was transferred to science to mean accurate and systematised knowledge. The Aristotelian theory of knowledge was the guide: you had "scientific knowledge" when you arrived at it demonstratively, not by experiment.

But with the beginning of modern science—first with the Copernican revolution in the mid-16th century, and then with the great age of science inspired by Galileo and Newton in the 17th century—the expression "scientific knowledge" came into use to distinguish this form of knowledge from common knowledge: that is, science and knowledge were coming to be regarded in England as no longer synonymous. Science came to stand for a particular kind of knowledge, whether derived by straight deductive logic (as in Euclid), or whether using observation and experiment (as in Bacon and Harvey.) But the full realisation of this did not come until almost the mid-19th century, as expressed, for example, in Herschel's *Discourse on the Study*

of *Natural Philosophy* in 1830.

In the 17th century, with the emergence of modern science, the new systems of the world began to be part of the education of the well-read person, and the new ideas were made available to the aristocracy and the middle class.

It was at this period that what has been described as "the first systematic written attempts at scientific popularisation" appeared. The first of the great popular expositors was Bernier le Bovier de Fontenelle (1657–1757). He must have been a delightful person. Voltaire considered him the most universal genius he had met. He was a rare person in his combination of scientific knowledge and love of literature. He was a nephew of the great Corneille, and a contributor to the *Mercure Galant*, a paper edited by another uncle, Thomas Corneille. He was appointed secretary of the Académie des Sciences in 1699, and like Oldenburg, the secretary of the Royal Society in London, he had wide contacts bringing him information on the new developments in science throughout Europe.

Fontenelle wrote particularly for the public of the "salons". His *Entretiens sur la pluralité des mondes* (1686) is in the form of a dialogue and is addressed to the needs of an imaginary marquise, "*jeune, aimable et ignorante*". His intention, he declared, "is to deal with philosophy (he means principally astronomy and physics) in the least philosophical manner possible; I have tried to develop it to a point where it shall be neither too dry for the gentry nor too superficial for the scientists . . ."

For Fontenelle, popularisation was a class matter. The *plebs* had no place in his dissemination. His works and those of the writers who followed him, such as the "*Spectacle de la Nature* (1732) by the Abbé Pluche, were primarily for the aristocracy, the wealthy bourgeoisie, and the ladies of the Court. The story is told of Fontenelle that one day at the Café Procope, the famous intellectual centre of Paris in the 17th century, he declared: "If my hand were cram full of knowledge, I wouldn't open it for the people". And on the sixth evening of his *Entretiens* he advises the marquise: "Let us content ourselves with being a select little band and not disclose our mysteries to the people".

In fact, the popularising of science to a general public could not come about until public forms of education had made literacy more general, until the media of dissemination were more widespread, and until there was a demand. People needed to realise that there was something to know which they were missing.

The *Entretiens* may have been written for a need already expressed: for example, Molière's *Femmes Savantes* was 15 years before the *Entretiens*, and his middle-class women spent evenings in their attics trying with a telescope to see the people on the moon. I do not regard Fontenelle as a populariser of science. He was a gifted propagandist for scientific ideas.

If Fontenelle was not a populariser, then who was? For an answer we need to go to the end of the 19th century when science was becoming established as a full time occupation for professionals.

During the early 19th century there were efforts—following the impetus of the industrial revolution—to make science available to such as mechanics, but the movement led by Henry Brougham, founder of the Society for the Dissemination of Useful Knowledge in 1826, to give working men a scientific education was doomed to failure; scientific knowledge could not be secured by superimposing instruction in the sciences upon a highly inadequate system of State education.

Similarly, the Royal Institution founded in 1799 to train mechanics, within a few years became a centre of scientific "entertainment" for a select few. Thomas Webster, who was Clerk of the Works in the early days of the Royal Institution, wrote to Count Rumford in 1799 with a proposal to found a school for mechanics in the house of the

Royal Institution. Rumford was delighted with the scheme and it was accepted by him—and by the Managers after some hesitations. But, by 1802, Webster had been granted sick leave and the project was abandoned. Why? I shall quote Webster's own words, but we must bear in mind that these were written in 1837, 35 years after the events, and Webster was by then an old and rather frustrated man. He wrote: "But this project for improving mechanics, well intended as it was, which promised to be so useful, and which had already gained for the Institution 'golden opinions' was doomed to be crushed by the timidity (for I shall forbear to speak more harshly) of a few. I was asked rudely (by an individual I shall not name) what I meant by instructing the lower classes in science. I was told likewise it was resolved upon, that the plan must be dropped as quietly as possible. It was thought to have a dangerous political tendency. I was told that if I persisted I would become a marked man."

The popular presentation of science was still designed for a few and not for the masses. The widely popular lectures of men like Huxley and Tyndall were of significance only to those who could read and write, and thus had little effect on the working masses.

Until recently the popularisation of science has been a class phenomenon designed for a privileged minority. Today we must rid ourselves of this concept of "popularisation". It smacks of the condescending, of Victorian do-goodism, of a patronising aloofness irrelevant to today's needs. We do not need to make science popular in a world in which science is of key importance. A single experience of space technology is more educative in this regard than millions of words. Besides, we cannot make science popular in the sense that Huxley and Tyndall wished to. The atom bomb has put an end to that. The catastrophic power of modern science confronts each one of us with profound moral issues. Further, the specialist fragmentation of science and its speed of change renders invalid the view that scientific ideas can be made clear through popular presentation. It was surely easier to popularise science a century ago when physics was largely a study of pulleys, levers and electric circuits; when chemistry consisted of reactions and formulae; and when biology was concerned with classifying different genera and species of plants and animals.

The trouble with most science writing—and in this I include all the mass media—is that we seek still to present science as a collection of facts. The mathematician, Professor Hyman Levy, commented: "The trouble about science and scientific explanation is that it tends to be incomprehensible to anyone except the expert". We must abjure the concept of popularisation in a democratic and rapidly changing society.

What we need then is more public understanding of science, and more public appreciation of the impact of science. This can only be achieved through a continuing education programme. The *raison d'être* of such a programme should be to help us to escape from the shackles of the scientific past; how to deal with new situations and how to find new facts; how to assess facts critically; and how to be one's own 'science critic' as well as football, or jazz, or music critic.

As we become more dependent on science, we become more vulnerable as the thing that has not been, and whose consequence cannot be foreseen, becomes the thing that is. Speedy and planned adaptation is already our need. It will become more, and not less, urgent. The social scientist has a key part to play here. I suggest there may be a law of social vulnerability, that is, a particular stage beyond which people begin to demand action at what seem to them to be "the harmful consequences of the application of science", for example, the social problems of air pollution, land conservation, use of pesticides, and urban development. If such a law can be found, then we shall be able to prevent

much misery, by securing corrective action before consequences become so gross that great quantities of antibodies—pressure groups of various kinds—are generated by the body social.

The populariser of science, as he functions today, cannot disseminate the subtle ideas of science. These really cannot be understood without hard, disciplined effort. It may be said that my reaction against former naive ideas about popularisation has gone too far. Of course, I am not against popularisation. I want a redefinition, a re-examination of the philosophy of popularisation. I believe popularisation of science must give way to wide public understanding and appreciation of science.

Who should be responsible for the necessary programme of activity? Clearly, it should be in considerable part a government responsibility. Just as the nation ploughs back a certain percentage of the gross national product to do scientific research, so it should invest a certain percentage of the research and development budget in public understanding of science, to help society to contend with some of the social problems that the applications of research and development cause.

What I have said are subjective impressions, generalisations for which I apologise. We need desperately in this country a research programme into the communication of scientific ideas to the public. Many millions of pounds are being spent annually for this purpose through press, radio, television, films, books, exhibitions, and museums. I have guesstimated that this sum is at least £20 million a year. Our ignorance about the impact of these media is complete. We know damn all. We have no objective criteria for assessing the social usefulness or effectiveness of these

media. We have only box-office and subjective generalisations. These are just not good enough.

I am happy that Glaxo is awarding, in collaboration with the Association of British Science Writers, four annual prizes of £500 each for popular science writing. I had hoped that from its inception there would be built into it a research programme. I say this because the American Westinghouse Awards for Science Writing, which have been running since before the Second World War, are useless in this respect. Their records are incomplete, and no one can say whether the Awards do more than put dollars into the pocket of some science writers each year—and provide publicity for Westinghouse. I would like to know how science writing and the communication of scientific ideas have benefitted. I apply the same criticism to the annual Kalinga prize for science writing administered by UNESCO—incidentally, an award I was proud to help into being when I worked at UNESCO.

The communication of scientific ideas needs a new approach. We have somehow to cope with a situation in which although politicians, and the citizens who elect them, continue to think in idea-proof compartments, the beliefs, values and institutions which nourish them are subject to rapid change. We need a new type of communicator, a modern Fontenelle, a poet and a visionary, a scientist and a visionary. He can help us to meet the flight from reason originating from the false belief—one that the popular communicators have failed to counter—of the threat of a blind, self-motivating, all-possessing, juggernaut of science and technology. I expect that then the alienation of people from science—the confusion in a “horror of lost self” as Robert Lowell sees it—will cease.

Practising science in Northern Ireland

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The practice of science in Northern Ireland is no harder than elsewhere but unwillingness to come to Northern Ireland because of exaggerated fears of the risks causes concern.

WHEN I was invited to write this article I accepted without much hesitation, but my experience has taught me that the provision of plain answers is not enough. Some of these may leave the erroneous and distasteful impression that scientists are indifferent to suffering. The reason seems to be that in spite of, or perhaps because of, the exceptional intensity of news coverage which Northern Ireland has received there is a general lack of any real sense of proportion about the violence and about how it affects work. To reduce the likelihood of being misunderstood in this way, I shall first present data enabling the scale of the violence in Northern Ireland to be viewed other than in isolation.

Comparing violence

Death is only one of the consequences of violence but it is both the most terrible and the most clearly defined. For comparison, the annual violent death rate will therefore be taken as a relevant and convenient (though admittedly oversimplified) index of the distress caused. Following standard practice with mortality statistics it will be expressed as the rate per hundred thousand inhabitants.

Table 1 gives data on death rates due to the troubles¹. In compiling it no attempt was made to distinguish guerilla deaths from civilian deaths proper but the former are officially estimated to number about one third of the latter. The locally recruited security forces (Ulster Defence Regiment, Royal Ulster Constabulary and Royal Ulster Constabulary Reserve) are grouped together as they are an integral part of the community. The method of presenting the rates obscures the danger to which members of these forces and members of the Army are exposed but nevertheless is appropriate as the total of the rates R_{NI} shown in the last row provides some indication of the impact of the violence on the people of Northern Ireland. Scrutiny of the table, with the knowledge that the total mortality rate in 1969 was 1,080.2 (ref. 2), should be reassuring to a rational man but I own it does not prevent me from fretting if a

Table 1 Death rates (per hundred thousand inhabitants) arising from disturbances in Northern Ireland¹

Year	1969	1970	1971	1972	1973	1974*
Civilian	0.8	1.5	7.5	20.9	11.0	11.0
Local security forces	0.1	0.1	1.0	2.7	1.4	1.8
Army	0.0	0.0	2.8	6.7	3.7	1.5
Total R_{NI}	0.9	1.6	11.3	30.3	16.1	14.3

The more recent figures were supplied by the RUC Press and Information Officer.

* Entries in this column are based on first 6 months of year.

member of my family is late in arriving home when bombers have been active.

An obvious comparison to make is with the civilian death rates from air raids on the UK during the Second World War. These rates, R_{AR} , are given in table 2. Their mean value 21.7 is less than twice the mean value 12.4 of R_{NI} which will be designated $\overline{R}_{NI}$, but this is quite misleading because the best known descriptions of the effects of the air-raids refer to the Greater London area where approximately half the deaths occurred and where the death rates were extremely high. A clearer appreciation of the position can be gained by excluding the Greater London area from consideration. The mean value of R_{AR} for the rest of the United Kingdom and $\overline{R}_{NI}$ are about equal. Destruction by a common enemy is of course easier to bear than destruction coming from within and arousing communal animosities.

Table 2 Civilian death rates, R_{AR} , (per hundred thousand) arising from air-raids on UK³

1940	1941	1942	1943	1944	1945
50.0	44.4	7.0	5.4	19.3	4.2

In the United States the murder (including non-negligent manslaughter) rate, R_M , is correlated with the population of the town or city⁴. This provides a useful gauge for the troubles here. Referring to Table 3 it may be seen that on average R_M equals $\overline{R}_{NI}$ in cities with a population of around a quarter of a million and equals the peak value of R_{NI} in the more notorious cities. As a garnish to the statistics I may mention that during the past 20 years, two members of the staff of my department have met with violence while in American cities (one shot at in Dallas because he witnessed a crime, another mugged in Los Angeles); neither of them has been injured as a result of the troubles—nor indeed as far as I can ascertain, has any member of the staff of the university.

Table 3 Murder rates, R_M , (per hundred thousand) in towns and cities of the United States (1970)⁴

No. of towns or cities in group	Population limits	Average population of member of group	Murder rate R_M
23,94	< 10,000	5,000	2.6
11,77	10,000–25,000	16,000	3.3
504	25,000–50,000	35,000	4.2
252	50,000–100,000	70,000	5.2
98	100,000–250,000	140,000	10.0
56	> 250,000	750,000	17.5
Selected cities			
	Philadelphia		18.1
	Houston		23.5
	Chicago		24.1
	Baltimore		25.5
	Dallas		28.7
	Washington DC		29.2
	Detroit		32.7
	Cleveland		36.1

The existence of very high murder rates in the United States causes much adverse comment but the existence of very high fatal accident rates R_A in many advanced countries passes almost unnoticed. Although fatal accidents are a greater hazard to life, they tend to be accepted apathetically as inevitable. A large number are undoubtedly inevitable because of human frailty but the width of the R_A range should kindle deep concern. Table 4 shows that the difference between R_A in England and Wales, where it is least, and R_A in most advanced countries is actually greater than $\overline{R}_{NI}$ (12.4). Fatal accidents are so numerous (almost 50 d⁻¹ in England and Wales and over 100 d⁻¹ in France) that though all are tragic, only a very small fraction are widely or vividly reported. In contrast, almost any violence in Northern Ireland may be widely and vividly reported because of the concentrated attention on events here.

Reluctance to come

A melancholy way in which the troubles have affected scientists in Northern Ireland is that people tend to be deterred from coming because they (or more often their wives or parents) are worried by the risks. The worry is not based on an objective appraisal of the risks such as I have attempted in the preceding section. It arises from repeatedly seeing Northern Ireland on television screens and in news items. People are indeed aware that these are, quite properly, highly selective. Nevertheless it is difficult to avoid becoming partly conditioned by them.

There have been cases of service engineers refusing to travel from Great Britain to Belfast and of firms putting such travel on a volunteer basis and being loath to renew maintenance contracts. The inconvenience caused has been of only a minor nature and any accompanying irritation has been amply compensated by the good conceit of ourselves induced by this display of lack of discernment and faint heartedness.

Table 4 Fatal accident rates R_A (per hundred thousand) in some advanced countries (1969 or 1970)⁵

Country	R_A
England and Wales (1970)	35.3
Northern Ireland (1970)	39.4
Japan (1970)	41.8
Republic of Ireland (1970)	42.9
Scotland (1970)	43.3
Sweden (1969)	43.3
Holland (1970)	49.4
Denmark (1969)	50.4
United States (1970)	54.1
Canada (1969)	55.4
Australia (1970)	55.6
New Zealand (1970)	56.4
Switzerland (1969)	58.2
Federal Germany (1969)	62.0
Belgium (1969)	66.0
France (1970)	74.3
Austria (1970)	78.5

Because of the troubles, a few university teachers have declined invitations to act as external examiners. The odd oral for a PhD candidate has had to be held outside Northern Ireland. Some external examiners have made enquiries about insurance cover while in Northern Ireland. Many have been apprehensive before their first visit. Feelings of apprehension, although unjustified, are entirely understandable and those who surmount them merit mild cossetting.

No difficulty has been found in getting visiting speakers for departmental research seminars. The practicality of holding major conferences here, however, has been uncertain. The Departments of Applied Mathematics and Theoretical Physics and of Pure and Applied Physics for example, obtained possession of attractive new buildings in September 1972. The five professors directly concerned had originally planned to mark the event by inviting the Institute of Physics to have its National Atomic and Molecular Physics Conference in the new buildings. But because of the disturbances they feared that attendance might be poor (though they did not doubt that distinguished invited speakers would come); and they decided unanimously to postpone the invitation. Perhaps they were over cautious. Certainly the Biochemical Society of London held a successful meeting here recently.

The Department of Zoology has observed a sad change in the willingness of groups to visit Northern Ireland. Before the troubles it established a Marine Biology Station near the entrance to Strangford Lough in County Down. A rich and varied fauna may be studied with the aid of the modern well-equipped fishing boat, the ecological diversity being unusually great because of the marked difference in exposure between the shores inside and outside the lough. Laboratory and residential accommodation for about 40 people is available and these excellent facilities were being enjoyed to an increasing extent by groups from other universities. That has virtually ceased.

Yet the Marine Biology Station is set amidst peaceful surroundings.

The most serious problem is presented by the number of students entering the Faculty of Science. In 1966 Queen's University, which from its opening in 1849 had remained an essentially local institution as far as its undergraduates were concerned, began to participate in the Universities Central Council on Admissions (UCCA) scheme in recognition of the fact that a considerable fraction of undergraduates both prefer, and are financially enabled to study away from home. An example illustrating the extent of the scholarly migration is that in October 1969 more than 25% of all entrants to the universities in the North-Western region of England (those in Lancaster, Liverpool, Manchester and Salford) were domiciled in the South-Eastern region⁶. Life in Northern Ireland had (and still has) much to offer, being engagingly (though alas now also agonisingly) different from life in England. In 1966 it did not seem unreasonable to expect that many students would elect to cross the Irish Sea and, indeed, by October 1968 the number entering the Faculty of Science from outside Northern Ireland had risen to 15% of the total. The troubles led to a drastic decrease in the inflow of students (and to some English students withdrawing at the insistence of their parents). Meanwhile the outflow, already substantial, continued to increase. Because of the imbalance the number entering Queen's Faculty of Science fell by 19% between October 1968 and 1973 whereas the number entering all faculties of science in the UK rose by 12% during the same period⁷. A turning may have been reached. Analyses of the UCCA application forms received by the end of June 1974 and June 1973, suggests that (against the national trend) the faculty may have more entrants in the coming academic year than it had this year.

The position regarding postgraduate students is happier. Between the academic years 1968–69 and 1973–74 the number in the Faculty of Science increased by 18%. This is actually 6% more than the corresponding increase in the total number of postgraduate students supported by the Science Research Council⁸ (which presumably provides a guide to the pattern in Great Britain).

Recruitment of staff is not easy. Fewer applications are received than for similar posts in other universities of the same standing and the practice of personally inviting applications from strong potential candidates has become less infrequent. The applicant who is offered an appointment occasionally states that he himself is eager to accept but that before doing so he must get the agreement of his wife who is worried at the prospect of living in Northern Ireland; and he may later have regretfully to write with the information that he has been unable to persuade her. The Board of Curators responsible naturally takes a long term view of the interests of the university and prefers to leave a temporary vacancy rather than make an appointment which is not fully satisfactory. A grave situation might have developed had it not been for the shortage of academic posts in Great Britain and the United States.

Carrying on

Some of the staff of the Faculty of Science have felt impelled to take part in communal or political activities—one (an applied mathematician) even ran successfully for election to the Northern Ireland Assembly. Their public spirited endeavours have inevitably been at the expense of their researches.

But what about the others, the great majority? I have asked many whether their researches have been affected by the troubles. All immediately replied that they have not and most seemed rather surprised by my question. A few expanded on their answer. Two added that any stress in life here is much less than the stress they had endured from commuting in London. Another, commenting introspectively on how little he was really disturbed by the sound of an explosion in spite of knowing that a tragedy may have occurred, said that except for a tinge of anger his reaction was mainly transitory curiosity such as he

might experience on noticing a speeding fire engine anywhere.

An objective (if objectionable) check on the validity of the opinion expressed on research can be obtained by comparing the number of journal publications per faculty staff member which are based on research likely to have been done during the first three years of the present troubles (the latest years known) with the corresponding number for the preceding 3 years. The former is less than the latter by 5%, which is not significant, being within the possible percentage error in either of the two numbers. Again, the computer power used in Queen's University has risen through the years of the troubles at almost precisely the same rapid rate as the total computer power used in all universities in the UK.

The staff of the faculty work and live in relatively safe areas. It would be odd if they let their researches be impaired in view of the resilience shown by much less fortunate fellow citizens. Traders whose premises are blasted soon put up 'Business as Usual' signs; factory workers have helped make possible the 23% increase⁹ in the Index of Industrial Production for Northern Ireland between 1969 and 1973 (which is rather greater than the 15% increase for the UK as a whole).

Evidence on the extent to which life here continues much more normally than people elsewhere seem to think is provided by the fact that most of our graduates still prefer to take up employment in Northern Ireland: on average 77.5% of those graduating in the academic years 1968–69 to 1972–73 did so as compared with 73.1% of those graduating in the academic years 1964–65 to 1967–68.

There is little which need be said regarding teaching. Some changes have been made in field work; for instance the Department of Geology judged it imprudent to continue to use a mountainous area just across the border with the Republic of Ireland, which it favoured before the troubles, because guerillas are now reputed to train there. Other geologically suitable areas are readily accessible. The Department of Geography has also modified its field work pattern—not as a consequence of any incident but to ensure that the risk of one is remote.

Members of the staff in charge of field work have unexcelled opportunities of getting to know their students really well. Those I have spoken to have not noticed tensions between the students nourished by our two different traditions. The student body as a whole has displayed a remarkably high standard of responsibility.

The undergraduates seem to have become more serious and to be working harder. Table 5 shows the number of those in the Faculty of Science who in a particular academic year leave without a degree expressed as a normalised fraction f of the number of those who graduate (the normalisation factor being chosen to make f for 1968–69 have the value unity). As may be seen f has been declining steadily through the troubles.

Table 5 Number of undergraduates leaving the Faculty of Science without a degree expressed as a normalised fraction, f , of the number of those who graduate in the same academic year

Academic year	1968–69	1969–70	1970–71	1971–72	1972–73
f	1.00	0.85	0.78	0.76	0.72

Examinations are particularly vulnerable to deliberate or casual interference but the troubles have had only a minor effect on those in the university. In June 1972, a chemistry examination was disrupted by a bomb hoax. Another examination was quickly arranged. This was done easily because the question paper for the supplementary examination to be held in September (for the benefit of candidates who failed) was ready. Since the disruption, security precautions have been taken in and around examination halls. These are so thorough that any hoax warnings can be ignored with complete confidence.

The recent general strike organised by the Ulster Workers' Council took place during the examinations. During the fortnight it lasted, 12,464 examination seats were to have been occupied. Only 35 were vacant because of the strike. On the day, May 20, on which travel was most rigorously curtailed the corresponding numbers were 805 and 8 respectively. Some candidates had to walk long distances; some were under severe strain. Contrary to expectation, however, the general level of performance does not seem to have been lowered.

By ill luck, the printing of the question papers, delayed by the three-day week imposed because of the miners' strike, had not been completed when the Ulster Workers' Council strike was decreed. For a few papers, manually operated typewriters had to be used to cut stencils and these had to be run through manually operated duplicators. That I should mention such a prosaic affair is itself a revealing final comment.

I thank numerous colleagues for their generous help. Professor F. J. Smith, Director of the Queen's University of Belfast Computer Centre, provided information on the rise of computer power.

- ¹ *RUC Chief Constable's Report 1973* (edit. by Committee of Police Administration) (Police Authorities Printing Unit, Belfast, 1974).
- ² *Statistical Office of the United Nations, Demographic Yearbook 1970*, 708 (Publishing Services, United Nations, New York, 1971).
- ³ *Whitaker's Almanack*, 79, 454 (London, 1947).
- ⁴ *Bureau of the Census, US Department of Commerce American Almanac (1973): The US Book of Facts Statistics and Information*, 145 (Grossett and Dunlap, New York, 1974).
- ⁵ *Statistical Office of the United Nations, Demographic Yearbook 1971*, 740-2 (Publishing Services, United Nations, New York, 1972).
- ⁶ *UCCA Statistical Supplement to the 8th Report 1969-70*. (The Universities Central Council on Admissions, Cheltenham, Gloucestershire, 1971).
- ⁷ *UCCA 7th to 11th Reports 1968-9 to 1972-3* (The Universities Central Council on Admissions, Cheltenham, 1970 to 1974).
- ⁸ *Science Research Council, Reports of the Council for the Years 1968-69 to 1973-74, Appendix III* (Her Majesty's Stationery Office, London, 1969-74).
- ⁹ *Statistics and Economics Unit, Department of Finance, Northern Ireland Economic Report on 1973*, 22 (Her Majesty's Stationery Office, Belfast, 1974).

Contrasting styles of social responsibility

John Hall

Social responsibility in science manifests itself in completely different ways in Britain and the United States. In Britain the emphasis is on words, whereas the American approach is based on deeds.

A DIVERTING and not entirely misleading illustration of Old World and New World attitudes to social responsibility in science and technology is contained in the following two exchanges. The first features Art Tamplin, one of four resident scientists engaged by the Natural Resources Defense Council (NRDC) in the United States, who, when asked what his agency is doing as protector of the environment, reaches for a list summarising 100 lawsuits and related activities undertaken by 14 NRDC lawyers during the first four years of its existence.

The second exchange takes place at Fortress House, Savile Row, home of the 150-year-old British Association for the Advancement of Science (BA), where the avuncular Secretary and sometime television personality Magnus Pyke throws up his hands and exclaims that one must be truly ignorant if one does not know already about the association's activities in the region of social responsibility. He then lists categories of BA activity, which include a meeting of members in Scotland, meant in some sense to introduce science to the nation, the consideration by members of the effects of science on the body corporate, and the organisation of working parties in which experts consider specific problems.

But earnest consideration apart, one asks, what is the BA actually doing, for example, in the area of environmental protection? Two or three operations are going on, concedes Secretary Pyke, centred on universities, and employing the services of groups of schoolboys acting as 'information agents'. What does this involve? "Well, they can run out and collect sediment, and seaweed, and so on. Rather like winning battles with the Pioneer Corps."

Contrast

The comparison is not made in an uncharitable spirit, but simply to offer broad paradigms of British and United

States responses to similar problems. In Britain the tendency is first to define and discuss the problems, possibly (but not necessarily) hazarding recommendations, after which one might publish abroad the findings of one's working party in the hope that somewhere in the course of the democratic process attention will be paid to the deliverances of one's eminent panel. Actively engaging a problem, head on, is not a popular tactic. The favoured approach assumes that the good sense and standing of the working party's members is recognised outside their academic sphere of influence by, say, an Energy or Environment Minister, who on the one hand might have read politics at Ruskin and on the other might have flunked classics at Balliol.

In America a socially concerned science group is more likely to reach for its lawyers or take a government agency by the throat as a first line of defence against malfunctioning technology; education, study-group organisation and publishing are likely to constitute a continuing but secondary strategy. The Old World approach is to deal with conundrums raised by the possibilities of new science; the New World's is to regulate its confrontations.



Art Tamplin, Gus Spech, and Tom Cochrane (NRDC)

The self-help ethic and frontier spirit aside there are good business reasons for the different tactics: in the United States there are six or seven times as many lawyers as in the United Kingdom, and a contingency fee system which allows them to take something like 25 per cent of a client's damages if they win, and nothing if they lose. Since no similar sporting arrangement is allowed by the British legal establishment, there is little incentive for pressure groups and lawyers to join forces; over here the barristers can afford to win or lose, and their clients can't afford to do either.

This is not to say that the British system of organising committees to make sage deliverances is ineffective; but since the main agencies operating in this fashion deal with generalised and long term problems rather than with questions of specific and immediate concern, there is less chance of establishing a casual link (or absence of a link) between the group's activities and the eventual policy line directed by the government of the day. Thus, if Professor Bodmer's working party on Social Concern and Biological Advances says, through the agency of the BA, that the government should be prepared to act in order to prevent the abuse of research on *in vitro* fertilisation, it is difficult for them to claim credit when the government does just that. It is not a singularly original recommendation to make in the first place, but even if it were, the working party could scarcely claim a copyright on the idea. The NRDC and the Scientists' Institute for Public Information, on the other hand, can quite clearly claim that the Atomic Energy Commission's \$5 billion liquid metal fast breeder reactor programme was brought to a standstill because of their objections: the Court of Appeals register for the District of Columbia says so.

The BA deliberately avoids such hand-to-hand combat and the taking of partisan lines on issues of the day. As Dr Pyke points out: "We're against instant wisdom. When somebody has just read about something in the paper this week, and they're marching down the street with banners on the subject, usually they're wrong, and puerile. The BA's approach, and indeed its main usefulness, is to make plain the issues and the facts of the issues; we're in the communications business." And the reason why it's wisest to present facts rather than taking sides, says Dr Pyke, is that a group of scientists is rather like the criminal classes, in that it represents a broad cross section of the community, with every variation of opinion and foolishness that this implies. "I've seen so many scientists make asses of themselves on their own time; there's no reason why they should do so on behalf of the BA", says the Secretary.

Accordingly, although the BA may set people to work at issues of concern to society—like the uses made of scientific innovations by the police, or the ethical and legal problems of biomedical advances—the combined pressures of arriving at a consensus, and of not 'taking sides' can result in findings which are unexceptionable to the point of being platitudinous. After studying police methods for recording and computer-banking information about individuals, a working party will say that "serious thought needs to be given to people's attitudes to the recording of information by which they can be identified"; or after studying the complex problems surrounding AID births, that "the status of children conceived through artificial insemination by donor needs to be legally defined". My milkman might have reached the same conclusions while sorting his change.

Influential

The only British group of any standing which goes gunning for issues of immediate public concern is Parliament's own Select Committee on Science and Technology, an all-party committee which, although it can do no more than call witnesses and make recommendations, has proved im-

mensely influential, not to say embarrassing, in the formulation of official policy on energy. Unlike some parliamentary committees, the science and technology group is not confined to a limited area of study; it has an open brief to investigate and report on whatever topic it thinks fit, and so it can offer a forum for all shades of opinion on issues which are the subject of imminent governmental action if it chooses.

This is exactly what it did when it heard last year that Mr Heath's government was strongly in favour of American light water reactors for the next generation of nuclear power production in Britain. By summoning its own series of expert witnesses it provided, in effect, a second-chamber debate on the issue. For although the only exchanges were conducted between each witness and the committee, the publicity given to the hearings encouraged witnesses to refer to the evidence of others, so that the proceedings developed very much along the lines of a debate.

The chief advantage that the select committee has over other social responsibility groups is that it has the full powers of Parliament "to send for persons, papers and records". In other words, if the select committee calls, you've simply got to attend, and when you're there you're obliged to talk. The practical difficulty the committee members face, of course, is knowing who has something to say, so that he can be summoned and obliged to say it publicly. During the nuclear reactor hearings, for example, Sir Alan Cottrell didn't actually step up and volunteer the information that he had doubts about the pressure vessel integrity of the American hardware. But a whisper was heard to this effect and he was invited by the select



Dr Jeremy Stone

committee to make public his reservations. Possibly they would have been expressed through departmental channels in the normal course of events, but if the select committee had not had its ear to the ground so that the vital evidence could be made public at a fairly crucial point in the debate, the outcome might have been less certain.

A further strength in the select committee's dealings is that its evidence is privileged. So, if you're called, say, to give expert evidence as an employee of the electricity supply industry, you can say with impunity precisely what you think about the way supply industry chiefs are running and planning the industry. For some witnesses, coercion to give evidence of this kind is a positive pleasure.

During the seven years of its hearings the select committee has helped to force the government's hand on various issues (including the creation of British Nuclear Fuels, the establishment of the National Nuclear Corporation, and the creation of a department dealing with population problems), and it has established itself as an irksome pressure group which it would nevertheless be difficult for any government to dismiss. It has had to walk the fine line between pricking a government's conscience and actually challenging its authority. Its overall aim, according to its Chairman, Arthur Palmer, is "to do solid work but not to take so long that our conclusions are out of date before they're reached, while at the same time not following fashionable issues to the extent that we're not taken seriously."

The remaining British groups lack both the Parnassian elevation of the BA and the exceptional powers of the select committee. Broadly, they concern themselves on the one hand with the ethical possibilities of new technologies, and on the other with fostering grassroots involvement to defend the proletariat against developments seen as harmful, and with the radicalisation of scientists to assist this counter-offensive. The first category is represented by groups like the Council for Science and Society (CSS) and the Science Policy Foundation (SPF), which operate a traditional learned working party/publishing machinery; the secondary category (unless you include broadly based groups like Friends of the Earth) is represented by a single body, the British Society for Social Responsibility in Science (BSSRS), which relies on a combination of proselytising and missionary expeditions. It is difficult to say which category is the least effective, since the groups variously claim that they deal in unquantifiable forces (ethics don't measure), they are relatively new (nothing to measure yet), or that worker involvement may in itself be progress, although its specific campaigns have been abortive (radicalisation doesn't measure).

Practical men

The Council for Science and Society was formed last year with the object of "promoting the study of and research into the social effects of science and technology, and of disseminating the results thereof to the public". A registered charity funded with £80,000 over three years from the Leverhulme Trust, its 43 members include the clutch of Fellows of the Royal Society whose eminent names are virtually *de rigueur* on councils of this kind, along with assorted lawyers, industrialists, moral philosophers, theologians and 'others'. The essential distinction between the functioning of the CSS and the BA, according to the council's moving spirit Paul Sieghart, is that the council operates with "men concerned with practical affairs", whereas the BA (Bodmer's group excepted) tends to think that a body of scientists can supply the answers. The founding of the council followed the publication in *Nature* of a paper by an inter-disciplinary working party convened by ex-mathematician and lawyer Sieghart to consider the scientist's social responsibilities. He was interested in the interfaces between the disciplines of theoretical

ethics and science—the areas where controlled experiments were out of the question—where, he says, it seemed that a gap was developing into which mankind might fall and which he was concerned to bridge. His working party felt that diffuse debate on the subject could be brought into sharper focus, and, to quote its literature, it sought to analyse what were the special social obligations of the scientists, and to devise some practical means for discharging them.

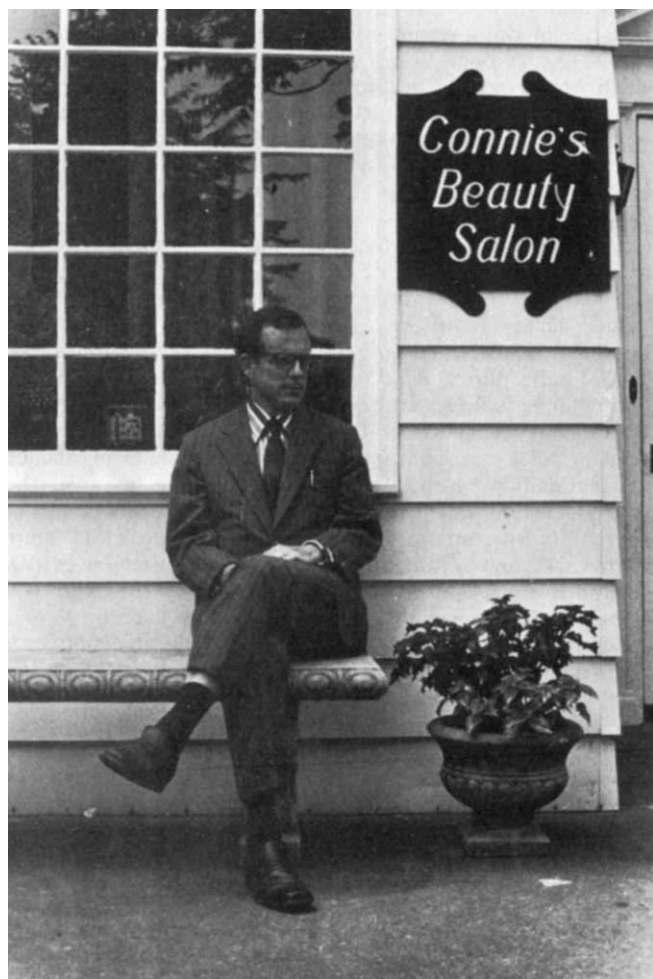
Its conclusion was that the primary need was for institutional machinery designed to identify problems in the field before they became acute, to stimulate well informed debate about them, and thus increase the time span for social decision making by the usual political process. Accordingly, the council is not a decision-making body, neither does it intervene in topics already well debated, or so far away as to border the realms of science fiction. Instead it "seeks to identify specific developments in science and technology whose social consequences lie just over the horizon, where no full scale debate has yet begun, but where intensive analysis of the actual and probable 'state of the art', and of the foreseeable social consequences can suggest a range of possible responses to those who will sooner or later have to take the necessary decisions".

Currently, working parties are discussing the standards to be applied and the procedures for applying them, in weighing 'acceptable risk' against anticipated benefits from new technologies; the use of surgical, pharmacological, psychological and other techniques for the control of individual behaviour deemed to be harmful or deviant; the problems involved in the development and use of 'harmless' weapons for the control of civil disorder; the problems posed to successful communication by the rapid growth in the volume of published technical information; the social and ethical implications of the nonclinical use of mood-control drugs; and the problem of monitoring technologies in those instances where technical competence is monopolised by a small number of institutions committed to the same interest.

The CSS will publish reports on each of these studies, outlining expected advances in the foreseeable future, the range of social consequences likely in the absence of controls, and the control mechanisms available if the consequences are to be modified. The overall aim is to arrive at an appropriate response "in the course of a responsible public debate conducted at leisure on the best information available, rather than by the hurried, ill informed and ill considered process which is apt to occur if the public does not become aware of the problem until too late in the day". Additionally, CSS makes itself available to government departments for advice, and apparently the appropriate departments have availed themselves of this facility already. On what issues? Confidential issues. Also, the council is available as confessor to scientists who have qualms about research projects they are working on. So far there has been one taker. On what issue? A confidential issue. The CSS probably has a rosier future than the BA in this area, because it engages younger, brighter people from mixed academic backgrounds, but for the moment there is nothing to measure but high intentions.

No criteria

The Science Policy Foundation (originally the Science of Science Foundation) has been operational since the middle 1960s, and has a similar difficulty in identifying its achievements, although in this case the claim is that there are no criteria for measuring the stock in trade: ideas, ethics, speculations. One thing abundantly in evidence at the SPF is a plethora of publications and eminent signatures in the guest book which also bears menus recalling the meals at which these eminents have taken their pleasures. The



Dr Jeremy Stone, outside the new headquarters of FAS

SPF looks like a one-man band, orchestrated by a former UNESCO science editor and *Reynolds News* writer, Maurice Goldsmith (although in fact he is answerable to a management committee). In 1964 Goldsmith was asked to edit a collection of articles to commemorate the 25th anniversary of J. D. Bernal's *Social Function of Science*. The collection was called *The Science of Science*, and after publication Sir Laurence Bragg, no less, suggested the formation of a Science of Science Foundation. No sooner was this said than done, with Mr Goldsmith at the helm, bearing a twin charter to look at science and technology internally in order to determine what were their growth mechanisms and to study the impact of science and technology on people.

To be fair, the SPF (the name changed because it became a bore to explain the meaning of the Science of Science at every turn) never actually undertook to do anything about social impact problems other than study them. In the event they have studied and published. Virtually everything the SPF touches involves a publication of some kind, and none takes a distinct line on a controversial issue. This is because the committee of management, which is another list of eminent names, covers such a wide spectrum of political views that no unanimous line emerges.

Two years ago the SPF set up a committee under Lord Avebury to take up contentious issues; the committee never reported. A similar committee was established to examine the Rothschild proposals for Government research and development; no agreed statement emerged, but the original report and the committee's deliberations over it were published, and sold. On energy the SPF takes the line that there is no need for an energy policy, but did not actually discuss reactor choices; on environmental pollution

it has made no statement, but, says Goldsmith, no member of the management committee would oppose the notion that pollution was a bad thing. Seminar fees, cash from publications, grants and donations roll in to the tune of £15,000 to £20,000 a year, and the prestigious dinner parties are entered in the book. "We do good by stealth," says Director Goldsmith, confiding that Cabinet Ministers receive "behind the scenes advice" at tables, where one may also find representatives of "key institutions", discussing things "pretty freely and off the record".

As a result of one tête à tête with Peter Walker (then Secretary of State for the Environment), Goldsmith and his colleagues at SPF were introduced to D. J. Lyons, Director General of Research Department of the Environment, and SPF was awarded the contract to publish the department's register of current research in the United Kingdom in the fields of town and country planning, environmental pollution, transport, building and construction. Not an insubstantial volume, but, says Mr Goldsmith, a non-profit making one.

Among the SPF's committees is one whose brief is to look at the foundation's terms of reference, with power to recommend that it be wound up if it is no longer a meaningful institution performing a useful function. The committee has never made such a drastic recommendation, although, says Goldsmith, if that's the way they feel, he hopes they will take the step. He adds that he doesn't expect this to happen while he is director.

The British Society for Social Responsibility in Science was formed at the Royal Society in 1969, with 40 Fellows among the founder members and a policy statement to which, it was said, the director of Porton could scarcely have objected. Most of the Fellows began to look worried when at the BA's 1970 meeting, the younger membership mounted a militant demonstration against British Army methods in Northern Ireland. A sort of Hippocratic Oath about scientists' moral responsibilities was taken by some members, and adopted as policy. Since then the society has agonised somewhat over its role and its political stance, and has emerged with a philosophy which says that moral oaths are pretty meaningless in a capitalist society, and that science is not simply a neutral body of knowledge, but a potent weapon for those who control it.

The abuses of advanced technology are not accidental, but spring from the nature of our society, says the BSSRS. Scientific and technical knowledge is "an important source of power, but only large institutions have the resources needed to exploit it. Advanced technology is used by our major corporations to create demand for new products, consumer or military. The government ensures, by economic management or direct intervention, that a market for these products will be found. . . . Thus science is used directly to increase the power of the already powerful and frustrate the expectations of the powerless". Naturally, the Royal Society Fellows are thin on the ground by now, but nobody at the BSSRS minds all that much, since, with the odd exception, Royal Society Fellows were found to be unwilling to do much more than lend their names to letterheads.

In terms of hard cash and administrative machinery the BSSRS looks distinctly shaky; its original Rowntree grant of £3,000 is almost spent, with no likelihood of renewal; membership stands at no more than 700 or 800; the society exists by courtesy of a largely part-time staff; and the £2,000 which it receives each year from endowments can be used only for educational purposes. Its office, also owned by Rowntrees, may not be available for much longer, and the work force is thinking of running the society as a collective. And yet these straightened circumstances, which might be the kiss of death to a traditional seminar/publishing-based body, organised on a centre-periphery administrative model, are less likely to kill a

loosely structured organisation like the BSSRS. It aims to develop an understanding of the social roles and functions of science and technology among people who do not normally expect to be consulted on such matters—the workers to whom its magazine *Science for People* is addressed—and its existence depends more on a network of grass-root operations than the survival of a central secretariat.

Already BSSRS scientists work in a consultative capacity with shop stewards' committees, mainly on issues like the toxicity or noise pollution of industrial processes—the strategy is to encourage people affected by technological nuisance to confront the problem themselves, with BSSRS supplying scientific expertise which the workers lack. They precipitated a strike by members of the National Union of Mineworkers over air pollution at a Coalite plant in Doncaster, action by a tenants' association attacking the plant responsible for the famous Battersea smell, and a strike by postgraduate workers at Edinburgh University which resulted in the raising of demonstration fees.

Urban collectives operate in Sheffield and Edinburgh, and autonomous BSSRS groups are active in half a dozen universities, beavering away at another favourite proposition of the society—that a non-elitist general education must emphasise the social implications of science and technology, and break down their isolation from other studies. All in all, the BSSRS might not be able to claim many successful campaigns against industry, but it can claim to have kindled community involvement, which is a success in itself, and it can only be a matter of time before its activities attract a grant from the Trade Union Congress.

Wide choice

In the United States there is an embarrassment of riches in the field of public interest science. An entirely arbitrary selection from the groups operating out of Washington yields the following bodies:

The Center for Science in the Public Interest (CSPI) operates a community involvement programme with aims similar to those of the BSSRS; the only difference is that it is more professional and more successful. The strategy is to introduce aggrieved citizen groups to experts capable of putting the finger on suspect planning decisions or industrial processes. Jointly with the public interest Economics Foundation, the CSPI has organised Professionals in the Public Interest, and come up with a meteorologist who helps groups to study air pollution from highways and power plants, an environmental engineer who is coordinating a survey of asbestos used in various consumer products, economists making evaluations of plans for interstate highways and cost/benefit analysis of public utility proposals, and a committee of scientists supplying community organisations with information on food additives.

The CSPI also has a healthy record running from asbestos to waste oil disposal, a list of 16 congressional and judicial testimonies last year, 48 administrative actions and requests, aimed at government agencies and individual senators, and two lawsuits, one requiring the Environmental Protection Agency (EPA) to reveal gasoline additives under the Federal Clean Air Act and the other attacking the EPA on asbestos, beryllium and mercury emission standards. Eleven major companies are opposing this action. The center's report on aerosols is thought to have cut market growth in that industry from 10% a year to 2½%.

This programme has been managed by a full-time staff of eleven, working for an average of \$360 a month, and a small army of volunteers. The CSPI started in 1971, with a staff of three working from a borrowed desk in the Oil, Chemical and Atomic Workers' office, and a budget of \$2,800 for the year. In 1972, the figure rose to \$19,600; in 1973 to \$39,600 and for the first nine months of this

year to \$72,600. Half of this money comes from the sale of publications and reports, the rest from foundations and donations.

Strategies, selected for the individual requirements of a problem, include the in-depth report, litigation, pamphletting, citizen organising and what is known as the professional informational approach. Latest successes included an investigative report, *Interlocking Oil*, on the power of oil executives who also serve as bank directors and who manipulate instruments to drive out competitors. Using this study, several senators are writing legislation to eliminate these conflicts of interest. The CSPI also helped to organise a citizen's energy conference in Washington for 1,000 citizen activists from 47 states to develop strategies for increasing citizen power in the decisions on the uses and costs of energy resources.

The Federation of American Scientists (FAS) was founded in 1946 as the Federation of Atomic Scientists and is the country's only scientific lobbying body. It has a staff of three, eminent sponsors who include 29 Nobel Laureates, and a membership of 6,500 lawyers, doctors, engineers and scientists whose membership fees amount to \$90,000 of 'hard' money annually. 'Hard' money is tax exempt, but not deductible, and so it can be used for lobbying, whereas the 'soft' kind can only be used for education and publicity that does not attempt to influence legislation. The FAS tradition of lobbying started in 1946, when its briefings of congressmen helped to ensure civilian control of atomic energy. More recent successes have included an important role in holding up the building of an antiballistic missile system, and pioneering work on the promotion of scientific relations and exchanges between the United States and China (the People's Republic, that is).

Through its Director, Jeremy Stone, the FAS button-holes congressmen, gets them to listen to informed scientific opinion, and testifies at hearings. Its tax-deductible subsidiary, the FAS Fund, engages in research and educational functions, including the publication of a Public Interest Report which has taken strong lines on SALT 1, electronic eavesdropping, national science policy, research and development priorities, the Geneva Protocol on biological and chemical weapons, and the rights of Soviet scientists.

Stone (son of I. F.) has just toured the States trying to raise \$1 million from a few rich men in order to endow positions for three scientists, probably retired professors, to develop FAS staff expertise in the areas of environment energy, medicine/public health, and development/population/food supply. According to the FAS the legislature hearings, although the heart of a publicly accessible debate over science and society issues, are often unattended by the press, and important laws get on to the books before alarms can be raised. The three new men will have the job of keeping an eye on such hearings, and making prompt reports, apart from providing briefings in their special fields at regular intervals.

The FAS, which calls itself the voice of science on Capitol Hill arranges two-way information exchanges between politicians and scientists, feeds congressmen's aides with intellectual grapes for scientific debates, and generally fixes things so that legislators do not make policies in areas whose workings they do not fully understand, without being fully aware of the alternative consequences. "We take positions on which reasonable men can hardly differ," says Stone. "We can't take eccentric lines; when you're going to Congress you've got to find the least common denominator".

The Natural Resources Defense Council, Inc., has a budget this year of £1,845,000. It employs four full-time scientists and 14 lawyers. It is four years old, and has a staff of 60 people working from headquarters in New

York, Palo Alto and Washington. It is the largest and most effective environmental law agency in America, and was founded to provide legal counsel to citizens and organisations seeking to protect the environment; to take legal action to protect the environment on its own initiative; to monitor the performance of government regulatory agencies whose activities affect the environment; and to encourage the legal profession to play a greater role in defending the environment.

In deciding whether or not to help citizen groups to find legal redress beyond their means in order to protect the environment, the NRDC uses two criteria: first; that the potential for establishing a legal precedent exists, and second, that without the NRDC's help, some valuable or unique environmental resource will be destroyed. Through

its recent actions it has saved for the time being much of the country's existing system of railroad track through a test case against the Interstate Commerce Commission, blocked the Atomic Energy Commission's liquid metal fast breeder reactor programme, forced the EPA to issue its standards on atmospheric lead standards, won a decision which challenged the clear-cutting of trees, sued to change the utility rate structures favouring big industrial users (granted by public utility commissions), opposed strip mining, offshore oil drilling and noise pollution in cities, and successfully petitioned the EPA to stop the use of four lethal poisons used by the Fish and Wildlife Service for predator control. To understand the full weight of the NRDC's effort you have to read the book listing its legal actions.

Murder involving discovery and first application of fluorescence of tyre prints

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Details are given from a murder investigation in which the fluorescence of tyre prints was discovered. The prints enabled the tyres and the vehicle in which the body was carried to be identified and fluorescence spectroscopy demonstrated a correlation between the fluorescence of one of the tyres and the corresponding print. Circumstances favouring the formation of fluorescent prints and the importance of the technique for forensic science are discussed.

PART of the evidence for the prosecution in a recent case of murder arose from the discovery by the investigating police officers of a set of fluorescent tyre prints. In our view the discovery will initiate developments of widespread significance to forensic science. We wish to describe, therefore, the circumstances of the case so far as they bear on this striking and hitherto unrecognised phenomenon.

The pertinent facts established in the enquiry, and subsequently accepted by the defence were that on the evening of Saturday, July 7, 1973, a Mini Estate vehicle, apparently deliberately set ablaze, was discovered in a field off Glasshouse Lane on the outskirts of Kenilworth. Immediate enquiries revealed that the owner was a local person, whose elder son, last seen that morning, proved to be missing. The son's bedroom and other parts of the house were heavily bloodstained. The investigation was therefore pursued as a case of murder, to be justified 5 days later in the discovery of the youth's body on a rubbish tip.

The parents of the youth had left home early that Saturday morning. At 0730h his younger brother was collected by a John Lees, who employed youths at weekends to assist in his work as a driver and labourer for a building company. Lees took the younger son to a building site, gave instructions on the work, and returned to the house, where he battered the still sleeping elder son to death. The body was rolled in the bed sheets, removed downstairs to the garage and into the family's Mini Estate vehicle, which was driven to a building site at Albion Street. Lees parked the car in number five of a newly completed and cleaned row of garages which he had worked on. That evening he drove to the tip, dumped the body on the tip face,

and covered the body with rubbish. He finally left the car ablaze in the field off Glasshouse Lane, and departed from the area. On his return 10 days later he was arrested, and subsequently, on January 21, 1974, at Birmingham Crown Court, pleaded guilty to the murder. He was sentenced to life imprisonment.

Our report concerns the Albion Street garage. Three days before the discovery of the body, when the movements of the car and any connections with Lees were crucially important matters, a bloodstained axe and a mutilated wallet belonging to the deceased were found close to the garages. There followed an inch-by-inch search that revealed in garage number five a small oil spot at the point expected had a front-engined car been reversely parked there. The oil proved to be largely Duckham's 20W/50, matching by thin layer chromatography and by fluorescence and infrared spectroscopy, oil from the Mini Estate. Otherwise, nothing whatsoever remained on the apparently featureless concrete garage floor to identify or to indicate even vaguely the type of vehicle that had evidently stood there.

It was decided that the floor should be examined in ultraviolet light. This was done with an Allen's portable lamp, emitting mainly at 366 nm, operated from a 12 V battery. Four brightly fluorescing tyre marks were revealed. (Figs 1 a and b). The precise definition of the marks enabled accurate measurements to be made that indicated, for the car concerned, a front track width of 122 cm, a rear track width of 117 cm, and a wheel base of 213 cm. Only Mini Estate vehicles correspond in these dimensions, for which the manufacturers quote 121, 116, and 214 cm respectively. The tread patterns reproduced in the marks are unquestionably of Goodyear G800 tyres at the front, and of Kelly Springfield KR1 tyres at the rear. The burnt-out Mini Estate carried these makes of tyres in the same positions. These results, together with the matching oil samples established a vital link in the chain of evidence.

Part of the front near-side mark and samples of nonfluorescent concrete were chipped from the floor and removed to the laboratory. Before the examination of this material, however, experiments were made to determine the origin of the effect, which, it was found, can be readily demonstrated. When a tyre is contacted with a strip of polyester-backed thin layer chromatography adsorbent (silica gel or alumina) for periods

of as little as 3 min, fluorescence appears at all contact points. The fluorescence is blue-green in colour (with excitation at 366 nm), varies slightly in shade between different tyres and adsorbents, increases with time and pressure of contact, and reproduces the tyre pattern in detail. Analysis of the fluorescent material (by chromatography on the adsorbent *in situ* by spectrofluorimetry *in situ*, and by the latter technique and by spectrophosphorimetry after solvent extraction from the adsorbent) indicates that the fluorescence is caused by the transfer of extender and process oils, antioxidants and polynuclear aromatic hydrocarbons from the tyre rubber to the adsorbent. All these factors vary with the make and the use of the tyres (J. B. F. L., unpublished) but the fluorescence originating from most tyres in current use is caused mainly by extender oils.

Figure 2 compares spectra from chloroform extracts of prints from a selection of tyres (Fig. 2a). The spectra, partly quenched by this solvent to increase the detail resolved, were synchronously excited at an interval of 30 nm (ref. 1). The sensitivity of our equipment to ultraviolet fluorescence was low and therefore the emissions recorded are those occurring mainly in the visible region. The spectra clearly demonstrated, however, the extent to which fluorescence can vary with the originating tyre.

The nature of the receiving surface determines the intensity of the fluorescence obtained. Level, fresh adsorbent surfaces, concrete or brickwork, for example, have exhibited distinguishable prints within a contact time of 8 min. On soiled or aged surfaces, or where tyres have been in repeated contact, no distinguishable fluorescent prints are formed. Repeated contact either produces a diffuse area of fluorescence, or transfers so much ultraviolet absorbing material that all fluorescence is

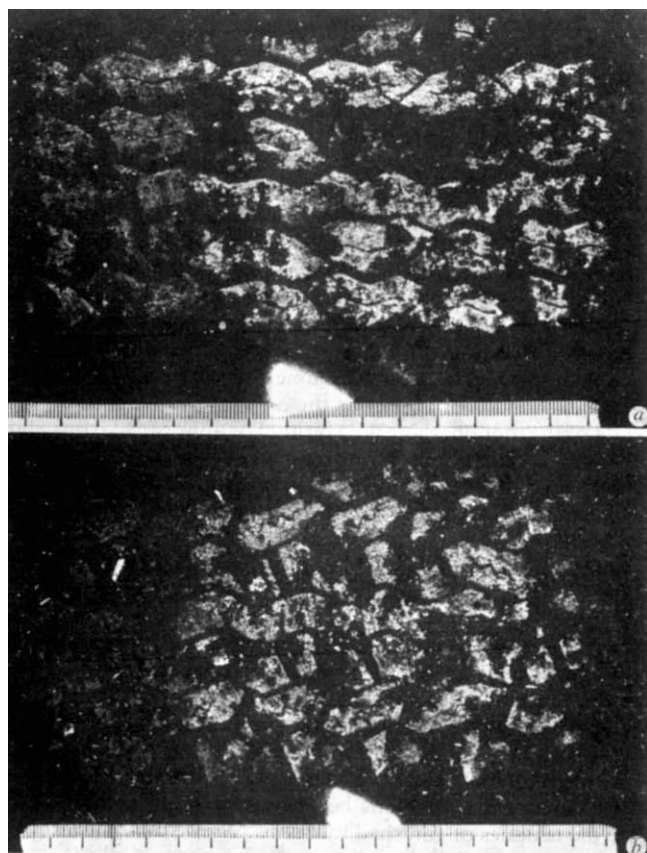


Fig. 1 *a*, Tyre print fluorescence, rear offside position at the Albion Street garage; *b*, tyre print fluorescence, front offside position at the Albion Street garage. Illumination in both cases was with an Allen's 12 V battery operated ultraviolet lamp. Photographed with a 35 mm single lens reflex camera fitted with a Wratten 8 filter on FP4 film exposed 600 s at f/5.6 and developed in Acutol.

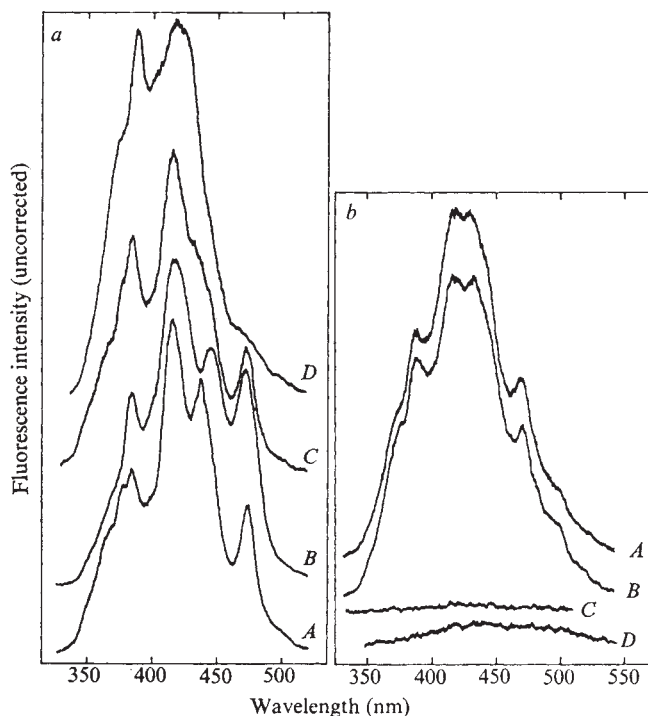


Fig. 2 *a*, Synchronously excited (30 nm interval) fluorescence emission spectra of chloroform extracts from prints, on silica gel, of various tyre samples: A, Michelin X; B, Goodyear G8 remould; C, Goodyear G8; D, Pleak remould. *b*, Synchronously excited (30 nm interval) fluorescence emission spectra of chloroform extracts of: A, nonfluorescent concrete from scene after contact overnight with tyre from Mini Traveller; B, concrete from fluorescent tyre print found at scene; C, concrete-underlying that used in B; D, nonfluorescent concrete from Albion Street garage.

quenched. Even so, many surfaces lie between the extremes. Thus, in our experience, fluorescent prints are often apparent in concrete-surfaced public car parks. No prints occur on bituminous surfaces, but many others, even of glass, collect material that, although not visibly fluorescent, yields fluorescent solvent extracts. For instance, a tyre dirt mark on paper is not fluorescent, but yields fluorescent solutions suitable for spectrofluorimetric analysis on solvent extraction. The effect is due to the minute particles of rubber of which such marks are composed (J. B. F. L., unpublished). That rubbers are intrinsically fluorescent has long been known, but this fluorescence, which is entirely suppressed by carbon black in tyre rubbers, is not extracted by organic solvents².

The circumstances at the garage were clearly ideal to the observation of tyre print fluorescence. Experiments made with a vehicle parked in an adjacent garage indicated that within 30 min four marks became apparent, after 1 h the fluorescence was considerably intensified, especially where the more heavily laden tyres contacted. This intensification continued over 8 h when all the marks had become equal in intensity. No visible changes occurred after this time, although the continued transfer of fluorescent material over extended periods of time can be demonstrated by spectrofluorimetry of solvent extracts.

Figure 2 also shows spectra from the material collected at the garage and from the corresponding tyre (Fig. 2b). The top surfaces of the chippings from the mark were scraped to yield 10 mg of powdered concrete, an extract of which in chloroform (0.5 ml) gave the spectrum shown. Further fragments of concrete, from the new surface exposed, contained no fluorescent material, in confirmation of the expected superficial distribution of fluorescence. Fluorescent material from the tyre was collected on nonfluorescent concrete taped to the tyre surface overnight. The spectrum of the extract obtained is also shown (Fig. 2b).

The excellent agreement shown in Fig. 2b between the two fluorescences added further weight to the highly significant evidence already obtained. We feel, however, that these results and the observations we have described will be important in many other circumstances. Apart from the characterisation of parked vehicles, examples, some already applied (J. B. F. L., unpublished), include the transfer of rubber from car accessories in hit and run accidents, from shoe soles and heels in scuff marks, from erasers to erasure marks, from the rubber debris contaminating surfaces heavily exposed to tyre contact

to people and articles themselves in contact, and, indeed, from any item liable to shed traces of rubber or fluorescent rubber additives at a scene of crime.

We wish to thank Detective Inspector J. F. Bradley of the Warwickshire Constabulary for the photographs reproduced and for experiments made at the scene.

¹ Lloyd, J. B. F., *Nature phys. Sci.*, **231**, 64–65 (1971); *J. forens. Sci. Soc.*, **11**, 83–94 (1971).

² Morris, V. N., *Ind. Engng Chem.* **26**, 107–111 (1934).

Objections to science

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Professor Cotgrove discusses the view that science is not as objective as its adherents claim. He considers the misuse of science, especially the use of pseudo-science to justify social practices.

RECENT years have seen a spate of critical writings on science. Much of this is concerned with the uses and abuses of science. But, some of the objections go deeper, questioning the objectivity and neutrality of science. Indeed, the Brook report to OECD went so far as to express concern at "the world-wide culture of educated youth which is deeply concerned with ecological perspectives and . . . could conceivably even adopt anti-rational views and could become more influential in the next decade than our extrapolations suggest"^{1–3}.

Science and culture

A dominant theme in the attack on science is its threat to humanistic values. The penetration of the world views of natural science into contemporary culture, it is argued, has encouraged ways of thought which will have disastrous consequences for the future of humanity. Specifically, it is the mechanisation and mathematisation of the world view of nature which is attacked: "Our hypnotic enslavement to the numerical aspects of reality has dulled our perception of non-quantitative moral values; the resultant end-justifies-the-means ethics may be a major factor in our undoing"⁴. Such objections in their more extreme forms go so far as a rejection of the primacy of reason and rationality and the celebration of emotion, feeling and unstructured spontaneity in thought and action^{5–6}. It is with such objections of course that the prevailing youth culture is so sympathetic and which may have particularly important implications for the future of science.

Those who see great dangers in the implications of science for human values have therefore sought to bring to light the meta-physical and ideological assumptions implicit in modern science and thus to challenge its claims to special objectivity. Second, they have exposed the ways in which science has been used as a justification and legitimisation for social and political policies (scientism), thus negating its claim to neutrality. It is to these issues that I now turn.

Mechanistic approach to nature

The nub of the debate is the argument that the influence of natural science on culture is to reduce man to mechanism. Post-Newtonian physics has all too successfully exorcised the ghost in the machine. In place of the 'primary' human experiences of taste, touch, sight, sound and smell, nature is now explicable to modern science only in terms of matter in motion, or more recently, forces and fields. So, the Baconian dream of mastery over nature for the "relief of man's estate" has been

turned into a nightmare in which science becomes the basis for the dehumanising not only of nature but also of man. In the last analysis, mind and human personality, purposes and values, freedom and dignity—all are reducible to matter in motion. Man too, as a part of nature, thus becomes the object of manipulation and control. The mastery of nature becomes the basis for the oppression and repression of all that is human.

The reaction, understandably, has been to challenge the hegemony of the mechanistic view in a variety of ways. A particularly powerful attack has emerged in recent years on the more simplistic positivistic views of science as being objective knowledge independent of human judgement. Some of this critique stems from historians of science who have investigated the actual process by which new theories come to be accepted in science. Distinguished scientists such as Medawar and Polanyi have similarly stressed the crucial role of personal judgement—the distinctive vision of the scientist who discovers a new way of looking at nature—often in spite of the facts. It is this crucial role of theory as a screen between the senses and 'reality' which makes science an essentially human and fallible activity, akin to artistic creativity in its higher reaches^{7–10}.

Such a perspective opens the way to an exploration of the external factors which influence the vision of the scientist as he seeks to interpret the shadows dancing on the wall. Thus, for example, Dijksterhuis concludes, "The strong influence which Newton's religious ideas exercised on his scientific thought is revealed, among other things, in his belief in the existence of absolute space and absolute time . . . Compared with the mechanistic idea of impact as the only cause of a change in the state of the motion, there is a spiritual or animistic flavour about the idea of an incomprehensible force operating at a distance which does not seem out of keeping with an anti-materialistic philosophy of nature." Needless to say, Newton's use of the concept force was strongly opposed by many of the leading natural philosophers of his day precisely on the grounds that it was an occult quality and unmechanistic (ref. 8, page 487 and ref. 11, chapter 7).

As an extension of this line of argument, the objectivity of the contemporary mathematical view of nature is questioned by asking what it is in fact that we now know about? Modern physics is a far cry from the attempts to understand nature in terms of the primary qualities ascertainable by the five senses. "Modern physics is not really concerned with 'things', but with the mathematical relations between certain abstractions which are the residues of vanished things . . . All we do in fact know is that we read our instruments—the number of clicks in the Geiger counter, or the position of a pointer on a dial—and interpret the signs according to the rules of the game . . ." (ref. 4, page 544). The 'facts' of nature are whatever meaning we can give to the readings on the dials. Or, as Bertrand Russell has succinctly observed, the only thing we know about the physical world is its mathematical properties.

Such observations then are used to support two main conclusions. Firstly, it is claimed, simplistic notions of the objectivity of science cannot be sustained. Galileo's view that "... the conclusions of natural science are true and necessary, and the judgement of man has nothing to do with them", is decisively rejected. Secondly, the limits and limitations of scientific knowledge are stressed. 'Certainty' is bought at the price of losing a massive amount of information and 'knowledge' of nature in the search for mathematical models.

Perhaps the weakest aspect of the challenge to the overriding dominance of the mechanistic view is its practical success, and the absence of any satisfactory notion of an alternative science. Here, the opponents of modern science turn to the recent history of science for examples of the way in which alternative views may exist side by side, each consistent with the known data. For example, Hesse shows that not only were theories of continuous action and action at a distance both equivalent in form and identical in experimental content, but both contributed to advances in electromagnetic theory (ref. 11, pages 216-222). It is argued too that alternative 'organic' views of nature have had some success in science. In the eighteenth century the divide between science and the humanities had not yet occurred, and speculation in natural philosophy embraced not only the experimenters but also poets and philosophers in its discourse including men like Shelley and Coleridge who turned to 'science' to combat the materialist mechanistic view. By contrast, they emphasised those aspects of science which stressed the unity of nature, the primacy of force over matter, and the unity of all forces. This Romantic viewpoint had an important influence on many scientists and in fact played a major part in the emergence of concepts of energy, and in many specific discoveries including the connection between electricity and magnetism, and Davy's discovery of potassium. In other words, an alternative paradigm free of the humanistic shortcomings of the mechanistic view has proved of value in the past and may do so again¹².

Reductionism and holism

Although modern physics is essentially reductionist, it is in biology where the feud between reductionism and holism has been fought with all the ferocity of a theological dispute. Monod, for instance, refers tersely to "a very stupid and misguided quarrel, which merely testifies to the 'holists' total lack of understanding of scientific method ..."

Although some of the protagonists dismiss the attack on reductionism as a return to vitalism, in essence, the debate is about whether we can explain the properties of complex phenomena solely in terms of the characteristics of the parts of which they are made; whether that is to say, there are emergent properties of systems that are not discoverable simply from an analysis of their components. The debate can be examined at two levels. Firstly reductionism can be tested like any other theory (or perhaps meta-theory) for its explanatory power. Secondly, and what is perhaps more interesting, the ideological undercurrents and implications can be identified.

The case against reductionism is explored intensively and extensively in *Beyond Reductionism*, the report of the Alpach Symposium at which a group of distinguished scientists explored the growing criticisms of much biological orthodoxy, and the 'robotomorphic' mechanistic view of man implied in behaviourist psychology. Weiss, for example, drew attention to a number of difficulties in the reductionist position. Analysis, he argues, by focusing on smaller and smaller parts, inevitably results in the loss of information, notably information about interaction between the parts. It is in this neutral sense, he maintains, that the whole is greater than the sum of the parts—that is, what is discovered and recorded about the parts by the process of analysis. What is lost is information about the orderly relations among the parts. We need, he argues, to take account of the regulatory and controlling mechanisms which are to be found in the larger systems of which the subsystem is a part¹³.

By contrast, Monod's reductionist emphasis looks at first sight to be dramatically opposed. This is in part a reflection of the fact that Monod's emphasis and examples focus strongly on the base of the hierarchy—on the regulatory mechanisms of DNA and the genetic code. But on closer examination, Monod's descriptions look less unlike those of Weiss despite the very different positions each have taken in relation to reductionism. Monod too speaks of microscopic systems, and of "the cybernetic system of the simplest cell", and "that all activities that contribute to the growth and multiplication of that cell are interconnected and intercontrolled ...",¹⁴. Monod too recognises that much remains to be demonstrated. But he decides as it were, to back a different horse.

It is highly probable that the issue will be resolved by further advances in microbiology. It is in any case an internal debate which will have to be left to the biologists to resolve. But of particular interest are the wider issues raised by the debate. Why, for example, are the protagonists so ready to accuse each other of such heresies as being unscientific, and so quick to identify the dogma in their opponents' positions? Both would seem to admit when pushed that neither position is dogmatically tenable and that the case is essentially unproven. For example, Commoner claims that the term 'central dogma' is often used in the literature on DNA. He quotes the opening comments of the chairman at the annual meeting of the Federation of American Societies of Biology (1965) as saying: "Let me review quickly the essential doctrines which comprise the dogma of modern genetics", and a participant as saying: "The reason we call this 'dogma' is that it depends on personal bias, not logic"¹⁵. Why then, if the tentative nature of theory is recognised, the impassioned partisanship?

Neutrality and commitment

In one sense, some measure of partisanship among scientists is what we would expect from what is now known about the process of discovery in science and especially the role of theory. But there are dimensions of this particular debate that are of special interest. For example, Monod has a section "dangers of genetic degradation in modern societies". This is the familiar argument which has raged since Galton and Spencer, that natural selection has been suspended. Monod's reasoning is worth quoting in full: "... statistics, as everybody knows, show a negative correlation between intelligence quotients (or cultural level) and the average number of children per couple. The same statistics also demonstrate that there is a high positive correlation of intelligence quotients between marital partners. This is a dangerous situation, which could gradually drain the highest genetic potential into an elite, shrinking in relative numbers"¹⁴.

Now there are two observations. First, this is a breathtakingly partisan statement and vast oversimplification of the nature-nurture debate about the nation's alleged declining intelligence. But more central to this discussion the reductionist position favours the 'nature' side of the equation—emphasising genetic factors rather than environmental influences.

What is being argued here is that such beliefs are embedded in and exemplify a more general ideology or *weltanschauung* which can be typified very crudely as antiliberal, and tough minded. The existence of such clusters of beliefs and attitudes is now well documented¹⁶. I am not here referring to the kind of ideological issues which have been traditionally associated with the left-right dimension in politics, but rather with a cluster of beliefs and attitudes which cut across such a conception of a conservative/radical dichotomy: in simple terms, an individual's attitude towards 'the bomb', and a range of 'Home Office' humane and moral issues. Thus support for the extension of nationalisation is no indication of a person's attitude towards capital punishment or the sterilisation of sexual offenders, or restriction on immigration. So it can be argued that support for the reductionist position is the expression of a more deeply rooted tough-minded philosophy of life, which not only values tough, logical rigorous and possibly rigidly linear thinking, but

is prepared to follow such logic to its perhaps disturbing conclusions, and in this sense allows means to determine ends and logic to dominate values. It is the expression of a basically pessimistic (though possibly realistic) view of human nature, aware of the need for tough and disciplined measures to control man's wayward tendencies and to nurture man's tenuous hold on civilisation. So, it would be claimed, we have to face the facts of the basic inequality of human genetic endowment and devise educational systems based on a recognition of such facts.

By contrast, it is those who incline to the opposite position, have a basically optimistic view of man's nature, and who locate the frustrations to the full flowering of human potential in impoverished environments and repressive social institutions, who are likely to find the implications of reductionism disturbing. Indeed, it is precisely from such radical critics of society and from the basis of the liberal-humanist tradition, that the most vigorous attack has been mounted—including Roszak, Dubos, and Habermas. From such perspectives, reductionism is seen as an expression of the mechanistic Baconian approach to science which sees science as a source of domination and control over nature (and man), as distinct from the more organic perspective of understanding and relating to nature¹².

Science as ideology

It is when the findings of 'science' are used as the basis for rationalising and justifying particular economic and political doctrines (scientism)¹⁷ that scientists are most open to attack for their partiality. There is a long tradition of justifying inequality, conflict, hierarchy, domination and competition through crude applications of biological notions to social dynamics (ref. 3, pages 259–263; ref. 18). Indeed, it can be argued that while crucial uncertainties are part of the human condition, there is need for folk sciences functioning as ideologies to provide comfort and reassurance. Seen in this light, the new natural philosophy of the seventeenth century "with its disenchanting and dehumanised world of nature and its appreciation of closely controlled experience, itself functioned as a folk science. . . ." And the extent to which 'science' persists as the dominant folk science can also be seen in the resistance to psi-phenomena as possible evidence of the powers of mind independent of matter, which if accepted would constitute a threat to the contemporary world view¹⁹.

Such scientism has entered a new lease of life with the current intellectual revival of ethology and its popularisation through such best-sellers as Desmond Morris's *Naked Ape*²⁰, and the earlier work of Lorenz. Despite the claim of the blurb that this study is "objectively scientific", Morris's book is in fact both partisan and prescriptive. Man is essentially a primate, the argument goes, and "still follows fundamental patterns of behaviour set down by his hunting-ape ancestors . . . and there is no hope of quickly shrugging off the accumulated genetic legacy of his whole evolutionary past". For example, the fact that *Homo sapiens* has evolved as the sexiest of all the primates is used to explain the fact that "whatever obscure, backward tribal units are doing today, the mainstream of our species expresses its pair-bonding character in its most extreme form, namely long term monogamous matings". So monogamy is safe: it's all in the genes; "the space ape still carries a picture of his wife and children with him in his wallet as he speeds towards the moon".

Now whatever the case for or against monogamy or the biological basis of religion, or aggression, the gap between genetic codes and such complex behaviour is so wide as to require a remarkable leap of faith to discover the bases of social relations and religious beliefs in the macromolecules of the DNA code. The most serious objection of the critics, however, is not so much that such claims put the objectivity of science into question, but that appeals to nature or to human nature are basically conservative. As Reich²¹ points out, they are used

to shift the problem from the social to the biological sphere where nothing can be done about it. Those who are anxious to change rather than to conserve, to free man from outworn constraints, to pursue new heights of discovery and self awareness, are understandably suspicious of theories which underpin a kind of fatalism; and an acceptance of what has been seen as natural, inevitable and in this sense, right²¹.

It could be argued that the attack on science is largely misdirected. It is the extravagant claims made for science which have generated a backlash. However elegant (and powerful) the mathematical equation, it is as partial to claim totality for such an approach to understanding nature as is the total rejection of science by those terrified at the prospect of a world without poetry. But science can hardly be blamed if some of its enthusiasts attempt a takeover bid for human culture. And if some scientists have used science as a pawn to promote the kind of world they want, one beyond 'freedom and dignity', or in which biological imperatives replace the messy and untidy human search for meaning and purpose, then they must not be surprised if such 'unscientific' behaviour stimulates some non-scientists to mount powerful antiscience arguments.

But to single out science as the cultural base for oppression, repression and various inhuman and antihuman policies is to overlook the repertoire of elaborate legitimations and justifications, both religious and secular that human ingenuity has invented for historical excursions into domination. It is one thing to point to the fact (with some justification) that science is and can be an instrument of human repression and quite another to argue that it is a major dynamic force marshalling the human race like the Gadarene Swine to rush headlong towards the destruction of all that is civilised.

Whatever legitimate criticisms can be mounted against the behaviour of some scientists and against some of the more simplistic versions of the nature of science, it can claim to be a special kind of knowledge in the very limited sense that it has been spectacularly successful in building a consensus of certified knowledge, which goes beyond the subjective judgment of any one individual. Whatever may be the human failings of individual scientists, and whatever the enthusiasms of the individual for his own theory, the success of science may lie in the way in which it has collectively regulated and harnessed the passions of such individuals to the shared enterprise of advancing public knowledge without deadening the enthusiasm necessary to sustain the often intense commitment to a theory. What keeps the individual creative scientist from being swept away by his own enthusiasm is the institutionalised code of conduct, which ensures that his work is subject to the critical scrutiny of his peers. It is at this level that for all its faults and blemishes, science can claim to have achieved a remarkably high level of objectivity. It is this quality of scientific knowledge which commands respect. The critics of science who question the objectivity of a science increasingly involved in military and industrial applications may well have a point. Such developments could conceivably damage the mechanisms of quality control²² and lose for scientific knowledge any special claim which it may have. And the antics of individual scientists who parade their ideological preferences under the guise of scientific objectivity outside the controlling mechanisms of the community of science, similarly threaten the high standards of their calling.

Beyond its more routine and humdrum reaches, science is an imaginative and creative act: the attempt to construct a meaningful picture of nature. And this is a picture which is in a constant state of flux and periodically undergoes revolutionary changes whenever a creative genius sees a new pattern in the ambiguous dance of the flames in the fire—a picture which excites the imagination of his contemporaries and generates a burst of activity to test its explanatory power. But in the last analysis the result is the subjective conviction of fallible men. What is accepted as a scientific truth is what survives the negotiations and interchanges within the scientific community. Whether and in what sense we can ever know 'objective reality' is a philosophical question beyond the scope of this paper.

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Science and works of art

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Over the past few years, considerable advances have been made in the application of scientific method to the conservation of works of art. Slow changes in paintings with exposure to light are still the subject of research but recent developments in the protection of outdoor sculptures are encouraging.

DESPITE much publicity about the intervention of science in the realm of art, comparatively few of the world's museums and galleries housing the fine and applied arts have their own scientific departments and the number of scientists engaged in this field is small compared with that of research workers on any subject of comparable breadth and complexity in universities or industry. Consequently, a particular technique or instrument may be available only in one museum laboratory in the world, not necessarily in Britain. The international scene in our special field of study is not densely populated and economic considerations are probably the limiting factor in the application of science to works of art.

There are three main areas of application: (1) examination to determine the physical and chemical composition of the object, the nature of past, present, and possible future deterioration and, on occasion, to aid dating or authentication; (2) conservation in the sense of providing the optimum environment to prolong the life of the object; (3) conservation in the sense of restoration, that is treatment of the object to repair existing damage or deterioration. Obviously all three are interdependent. For example, examination is a prerequisite of treatment and to return a treated object to an environment which does not minimise the risk of future damage is to nullify in part the benefits of restoration.

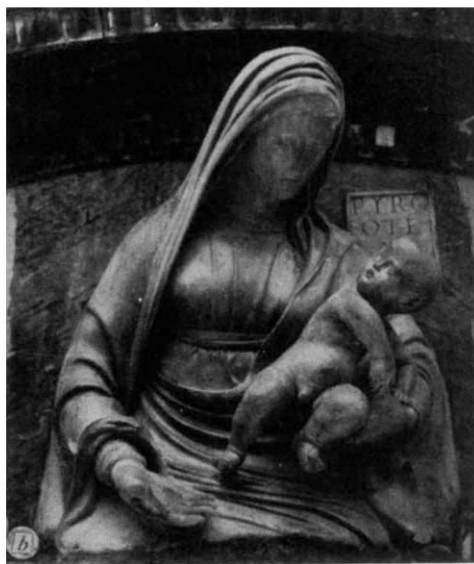
Paintings

European easel paintings, the kind seen in the National Gallery, London, and usually dating from about 1300 onwards and painted on wood panel or canvas, are a rather special category. Every component of the multi-layer structure which comprises a painting—wood, canvas or metal of support, ground or priming layers, pigment

and medium of paint layers, varnish or surface coating—can be subjected to scientific examination, and the layer structure itself merits close study. Although such examinations often aid conservation and sometimes research in art history, it should be stressed that the study of artists' materials and techniques is a proper subject in its own right.

Starting with the lowest layer of the picture, the support, identification by microscopical methods of the wood species used in panels gives an indication of the provenance of the picture, but little hint of its date. Carbon-14 dating, indispensable in archaeology, is not usually applicable to painting because of limitations of sample size and the small time-span involved, but an allied dating technique—dendrochronology, the measurement of annual growth rings of trees—has proved useful. First applied in Hamburg to panel paintings of Rembrandt and Wouwermans, the technique has been developed at the Research Laboratory for Archaeology and the History of Art at Oxford where a new reference curve for slow-grown oak has been compiled and measurements made on oak panels including paintings by Holbein and Rubens in the National Gallery and National Portrait Gallery¹. The quarter-sawn planks often had 200–300 rings. For pictures independently dated, the tree-ring date usually worked out to be the date of painting plus about five years for seasoning of the wood. Unfortunately the technique is unlikely to be extended to Italian panel paintings since these are mostly painted on poplar wood.

One of the most important developments has been in the identification of paint media which up to about 10 years ago could only be roughly classified. Gas chromatographic analysis, pioneered by the National Gallery laboratory² is now used in several other museum laboratories in various parts of the world to detect the fatty acids present in dried oil and egg films, the ratio of which indicates whether oil or egg was originally present and the type of drying oil. It was found, for example, that Piero della Francesca's "Baptism" was painted in egg tempera, but his "St Michael" in drying oil, specifically walnut oil. Occasionally different areas or even different layers of the same picture have different types of medium. For this reason it is as well to use some microscopical technique,



Virgin and Child by Pyrgotelis, Church of St Maria dei Miracoli, Venice. *a*, Detail before treatment, *b*, after cleaning and consolidation (carried out by K. Hempel, Victoria and Albert Museum, London, and G. Musumeci, Venice).

such as biological staining, on a paint cross section before analysis. Although ^{14}C dating is not generally used, detection in the United States of recent forgeries, even of late 19th century pictures, has proved possible by measuring the increase of ^{14}C in artists' materials—in this instance linseed oil—resulting from the atmospheric testing of nuclear weapons³.

Identification of pigments is still often done by well established methods of chemical microscopy, a less arduous exercise than it would seem in that the majority of artists' pigments in the past were simple compounds of metals such as oxides, carbonates or sulphides, or minerals or other crystalline materials having well defined particle characteristics and optical properties. Emission spectrography and X-ray diffraction have also long been used, the latter indicating the compound present rather than the elements only. The electron microbeam probe would be ideal for layer-by-layer analysis of the mounted paint cross section but its cost and complexity prevent its acquisition. Over the past decade we have been grateful to have occasional samples examined on instruments belonging to other institutions but a long run of coordinated samples is needed for significant results when buying or borrowing time on an instrument. That it can be done successfully is proved by a paper published by the Louvre laboratory on the scanning of sections of early Italian paintings⁴. Lacking an electron microbeam probe on the premises, the National Gallery has just acquired a laser microspectral analyser. The use of laser microspectrography in analysis of works of art was introduced in the laboratory of the Boston Museum of Fine Arts some years ago. In the apparatus now in London the laser is used to evaporate a minute amount of the sample, thereby forming a crater the dimensions of which may be varied between 10 and 100 μm . The firing of the laser is arranged to coincide with the sparking of carbon electrodes and the rest is emission spectrography.

All the above methods require removal of a sample, however small, so a non-destructive method of scanning the surface of the painting for elements is desirable. X-ray fluorescence analysis is an obvious choice, with hopes pinned on the energy-dispersive form. Even here the layer structure cannot be ignored for the primary X-ray beam may penetrate the uppermost paint layer with confusing results. Also the range of elements is greater than in, say bronzes or silver coins. Sensational in their possibilities are a whole range of analytical techniques based on the application of nuclear energy, again a facility not to be found in the museum itself. In the mid 1960s work was carried

out in both Delft and Munich on neutron activation analysis of trace elements of lead white. Results indicated variations not only with date but also with geographical location. In the United States autoradiography of paintings has been used to identify pigments, as has isotope mass spectrometry, and one method for dating lead white depends on measuring its natural radioactivity. It is an achievement in itself to have evolved or applied these techniques. One hopes that these will not be isolated experiments but the start of some serious data collecting. The Doerner Institute at Munich recently put out a paper in which the author had compiled a table of periods of use and terminal dates of artists' pigments from his extensive experience of analysing pigments from a vast number of pictures of different schools and dates, using fairly traditional methods. Simultaneously with analytical methods examination of paintings by X radiography, infrared and ultraviolet photography still goes on. A recent advance is infrared reflectography, developed in the Netherlands particularly for revealing carbon black underdrawing on white grounds. It involves the use of infrared light at a wavelength of about 2 mm and an infrared-sensitive television camera instead of infrared-sensitive plates or film⁵. The National Gallery in London now has such an apparatus. The need to control the humidity and temperature of the atmosphere in which paintings are hung, particularly wood panel paintings, was recognised as long ago as the 1930s, and the first fully air-conditioned room with humidity control, cooling, warming, dust filtration and removal of SO_2 was opened in the National Gallery in 1950 to house some of the most important panel paintings. Eventually all the west wing was air conditioned. Control of illumination took longer to gain acceptance. Now, in addition to having ultraviolet filters on all light sources, whether daylight or artificial, the visible light has been reduced to 150 lx. Obvious damage by light is fading of pigments and dye-stuffs but photochemical degradation of any organic component, whether medium, varnish or canvas, is also likely to occur. It is often assumed that after a hundred years or so paintings must have reached some sort of end point in the changes of colour they may undergo. There is no objective evidence for this assumption. In rare cases where part of a picture has been protected from light the contrast with the exposed part is alarming. Research has been going on in the National Gallery to find methods of recording very slow changes in colour of paintings. The recent acquisition of a reflectance spectrophotometer, designed for the purpose by W. D. Wright, is a significant step

forward. The new extension to the National Gallery which is to open next year, will have temperature, relative humidity, sulphur dioxide and light levels automatically controlled and recorded by a data logger for future use, but there can be no cause for complacency while the east wing of the present building still lacks air conditioning.

Restoration

In the treatment of paintings science plays rather less part than is the case for other types of works of art, for example objects of metal and stone. Although it might make his task less hazardous and certainly more interesting, it is doubtful whether a knowledge of the mechanism of polymerisation of drying oils or the optics of paint films would enable a picture restorer to produce a visually satisfactory final effect in cleaning, retouching or varnishing a picture. There seems to be no substitute in this case for skill and experience. In the postwar years it had seemed likely that modern synthetic materials of a high degree of stability would replace the traditional natural materials used in picture restoration. This expectation was only partly fulfilled. In this country at any rate restorers often show reluctance to use as varnishes or retouching media materials which differ markedly in handling properties from those they are accustomed to, and this includes some polymers with otherwise desirable properties, for example polyvinyl acetate and some acrylic copolymers. For final varnishing many prefer the lower molecular weight polycyclohexanone resins despite the fact they have only a modest advantage over the natural resins in rate of discolouration; their handling qualities are, however, similar. On the backs of pictures modern synthetic materials are more frequently used, for example the non shrinking epoxy resin adhesives instead of animal glue.

Recently the standard treatment of canvas supports, that of sticking a new canvas on the back of an old and weakened one to strengthen it, has come under scrutiny. Lining of canvases dates at least from the late 17th century, the earliest adhesives being glue and flour paste, in this century frequently replaced by beeswax mixtures. Now in its turn the soundness of wax lining has been questioned and in April this year a three-day international conference met at the National Maritime Museum, Greenwich, to discuss lining techniques. Alternative types of adhesive were proposed, such as emulsions of vinyl polymers, and lining canvases of polypropylene or glass fibre were demonstrated. Also on show were improved types of vacuum hot tables which enable lining to be carried out without the heavy ironing previously needed. One of these had been designed at the Courtauld Institute of Art, University of London. Although no clear-cut resolution seems to have been taken in favour of any one method the conference was an opportunity for discussion of a rather neglected but necessary aspect of restoration.

For art objects, technical examinations has been directed towards problems of dating and authentication, supplementing the art historian's style criticism, and towards investigating details of structure, composition and condition. Those methods which supplement visual examination—optical microscopy, X radiography, ultraviolet fluorescence and infrared photography have of course been available for many years. Wet chemical analysis has been in use since the 19th century for metal objects. The methods of physical analysis, developed mainly since 1900 and particularly since the Second World War, are applicable as much to art objects as to those usually regarded as falling within the field of archaeology. They have been used more sparingly in museums specialising in post-classical material where there is still a certain reluctance to turn to scientific aids, particularly when sampling is involved.

Of the methods of absolute dating and the consequent possibility of authentication where stylistic evidence and details of provenance are insufficiently positive, three of the methods of the archaeologist are available: ^{14}C dating, dendrochronology and thermoluminescence. It is seldom feasible to use ^{14}C dating for art objects of comparatively recent date, while dendrochronology though applicable for example to the study of furniture and wooden sculpture does not seem so far to have been used for the former, and not extensively for the latter. Neither of these methods is in any case linked directly with the date of production of the art object. Much interest has been shown, however, in the technique of thermoluminescence (TL) for absolute dating and the detection of fakes in ceramic objects, this has been developed at, among other centres, the Research Laboratory for Archaeology and the History of Art at Oxford. The techniques were until recently of value mainly for dating pottery more than 500 years old. Advances since 1969 have extended the range to more recent times⁶. A study of authenticity of Italian Renaissance terracottas, in comparison with documented forgeries of high quality by a nineteenth century sculptor, has demonstrated the possibilities of solving problems of recent art history, though unfortunately not to the extent that the work of master and pupil can be distinguished. These methods have been used during the past few years for an extensive study of Chinese Tang dynasty ceramics (618–906 AD) with good dating results for genuine works and clear distinction between these and imitations.

Most of the physical methods of analysis of value in archaeological research find a use in attempting to solve particular problems in the decorative arts, though extensive studies of groups of objects of particular periods, districts or craftsmen, sufficient for making judgements for inclusion or rejection of doubtful pieces on analytical grounds, are rare. Moreover, comparison between analytical results from different institutions is often of dubious value because of differences in sampling techniques and absence of information on precision and accuracy. Of the methods available (which there is no space to list in detail here) X-ray fluorescence analysis, being non-destructive, is naturally attractive to the curator of valuable art objects, though the fact that it is less accurate than atomic absorption spectroscopy and that analysis is only of the surface layers of an object, which are usually of different composition from the body of the object, make its use less valuable, except for specific studies of superficial layers. Recent attention both in the United Kingdom and elsewhere has centred on the development of energy dispersive X-ray fluorescence spectrometers. Their increased sensitivity compared with crystal dispersion types makes it possible to use radio isotope sources or miniature X-ray tubes, thus imparting a degree of portability, and the multi-channel analyser greatly increases the speed of analysis. One form of this apparatus, the Isoprobe, referred to above in connection with paintings, and developed at the Oxford laboratory⁷ has recently begun operation as part of the York Glaziers' Trust Research Programme for studying the chemical composition of 12th century stained glass from York Minister. Most analytical methods require a sample such as a fine drilling from an unobtrusive part of an object, but the X-ray diffraction techniques described by Bimson⁸ for examining the crystalline constituents of soft and hard paste porcelain for authenticity or attribution requires a sample so small that the method could be almost described as non-destructive.

Environment

In a modern museum of the decorative arts, the tendency to display in one gallery art objects of every kind of a

particular period provides problems of environmental conservation over and above those of a gallery of paintings alone. The control of light levels, of vital importance for textiles, where both dyestuffs and their fabric substrates are damaged, is made difficult by the complexity of the 'visual problem' of local lighting for particular objects and reflections from show cases, so that disability glare factors impel the curator to call for light levels higher than the 50 lx generally accepted as desirable⁹. The problem of damage by light was first studied scientifically at the Victoria and Albert Museum (then the South Kensington Museum) in 1888. Studies relevant to paintings but also of general value have been made continuously at the National Gallery since the 1950s and experiments on the fading of textiles, begun at the Victoria and Albert Museum in the 1960s are continuing.

Requirements for temperature and relative humidity and the elimination of air pollution are broadly similar for most art objects even though the properties of particular objects may require localised conditions. For the general ambience the tendency, where it is possible, to install complete air conditioning is to recommend more complete elimination of pollutant gases, notably sulphur dioxide, than previously specified, and, particularly where textiles are involved, the elimination of a high percentage of grime in the submicron range (60% plus on test dust No. 1).

Turning to the many problems of the restoration of art objects, apart from those which require fine craftsmanship in repair work, specialists in the United Kingdom are taking part in notable developments in stone¹⁰ and textile conservation while close attention is being paid to problems of deterioration and protection of painted and stained glass¹¹. British workers are in the forefront of developments in these fields. One of these, the problem of arresting the decay of calcareous stone and marble sculpture (and more generally the stone of buildings), in modern industrial atmospheres was, as recently as 1963, declared to be insoluble¹². Consolidation treatment when the sculpture could be brought indoors was confined to wax impregnation. Deterioration out of doors is a consequence, still not fully understood, of the complex interaction of a more or less porous aggregate containing calcium carbonate, with water, carbon dioxide and sulphur dioxide together with soluble salts, including, in some situations, sodium chloride. If the sculpture can be brought indoors consolidation treatment is usually needed, in conjunction with cleaning. If the sculpture must remain *in situ* total loss of the object as a work of art must be expected eventually unless treatment is given. Recently, notable advances in treatment have been made and the prospects are now

brighter than in 1963. Consolidation inevitably involves impregnation with a material which enters the pores of the superficial deteriorated layers, preferably penetrating into or bonding with the sound stone beyond. Dutch and American investigators have been using selected epoxy resins, vinyl fluoride polymers and silicon esters and successful work has also been done with a solution of barium hydroxide and urea leading to the deposition of barium carbonate. A different approach has been adopted for external sculpture in Venice by English conservators¹⁰ who apply a monomer of trimethoxymethyl silane which penetrates easily and deeply into marble and polymerises with water to a hard cross-linked solid *in situ*.

In 1950 the late F. I. G. Rawlins, then Scientific Adviser to the National Gallery, announced in *Nature*¹³ the formation of a new international institute for the coordination and advancement of research in conservation. This was the International Institute for Conservation of Historic and Artistic Works of which he was Secretary-General for some years until one of us (N.S.B.) took over that post. The institute, which celebrates its 25th anniversary next year with its sixth international congress, in Stockholm, has its headquarters in Trafalgar Square, London. Its quarterly technical journal, *Studies in Conservation*, first published in 1952, contains original work and reviews on advances in conservation and restoration. This with its *Art and Archeology Technical Abstracts* (twice yearly) and the publications arising from its congresses enables its world-wide membership, which includes most of the world's leading conservators, to keep abreast of developments.

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⁷ Hall, E. T., Schweizer, F., and Toller, P. A., *Archaeometry*, **15**, 53 (1973).

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¹⁰ Hempel, K., and Moncrieff, A., in *The Treatment of Stone* (Centro per la Conservazione delle Sculture all'Aperto, Bologna, 1972).

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¹³ *Nature*, **165**, 903 (1950).

Rutherford's Cavendish

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Sir Edward Bullard recalls his early days at the Cavendish Laboratory in Cambridge where, under the watchful eye of Lord Rutherford, he worked, and struggled, as a research student in the company of people like Blackett, Kapitza, and Cockcroft.

I FIRST saw the Cavendish nearly 50 years ago, in December 1925, when I made an unsuccessful attempt to get a scholarship. The physics practical exam was held in the large room to the right of the arch as you come in. I was

a little surprised to find that my galvanometer was permanently jammed and that the assistants and demonstrators did not think it at all odd. Indeed, it was not odd: most of the equipment in the lab was like that.

The following year I went up to Clare and embarked on the Natural Science Tripos. I found the Part I Physics lectures deeply disappointing. Alex Wood, on mechanics, roughly covered the first book of the Principia and the Cavendish experiment, together with a little about gyroscopes. I found that the lack of generality and the attempts to avoid all but the simplest calculus were tedious. I went off



Mr. F. Lincoln, the head of the Cavendish workshop

Cavendish Laboratory

to listen, a little uncomprehendingly, to Pars on analytical mechanics, and also, very briefly, to Larmor. By part II the lectures had become better and they gave a sense of contact with contemporary physics.

It was, I think, early in my third year that, coming out of a lecture, I met Patrick Blackett who asked me what I was doing. I replied that I had been listening to Aston talking about mass spectroscopes. "Why?", he said, "everything he says is in his book". It came to me as a revelation, and I went to no more lectures, except to Rutherford, whom I could not resist. He would boom on, talking about all kinds of interesting things, occasionally producing gems like "integral $y \cdot dx$; dx is small, we will neglect this". He talked so easily and informally, he knew it all in an instinctive, relaxed way and the answer always somehow came out right. As someone said: "The α particles were his friends, he knew what they would do" (there was a story, which I have not verified, that in one of his early papers the mass of an α particle came out as 3.3 on which he commented: "we take four as the nearest integer").

Although the practical classes interested me I learnt almost nothing useful in them. A practical class can serve three purposes: it can teach the techniques of measurement; it can allow the student to go over the path by which the principles of physics were discovered; or it can help to give contact with contemporary physics. The practicals in the Cavendish were largely historical, tempered with some feeling that, if the equipment was available (which it wasn't), there ought to be some experiments on modern physics. As it was, we swung pendulums which had their bobs in buckets of water and tried to find the frequency of a tuning fork with a phonic motor once used by Lord Rayleigh. (The usefulness of that potentially interesting experiment was reduced by the absence of a clock that could match the stability of the tuning fork.) The trouble was, I suppose, that there was very little money for equipment and that most of the very able and distinguished men running the classes had more important and exciting things to do. Indeed, when, in my third year as an undergraduate I tried to devise some new experiments for the Part II class, I found every encouragement and immediate acceptance of innovation.

I think the physics course in the 1920s was, in an important way, preferable to that of today. It was not very difficult. A reasonably intelligent man, who was interested in the subject, who took pains to understand it, and who could write in a way that would show that he did understand it, could get a first in the tripos without wearing himself out or concentrating too exclusively on science. He could take up politics or hiking, or learn a foreign language, without feeling that he was not giving enough time to physics.

In the Cavendish one absorbed an attitude to knowledge,

and an intellectual style. A real physicist ought to be able to estimate any quantity within a factor of 10 without looking in a book, using only a pencil and the back of an envelope. The central idea was that when you really understood anything it would seem simple. When I was an undergraduate, this spirit filtered down through research students a few years older than I was, particularly through Jimmy Braddick, who was in a constant state of indignation about things that Rutherford had said to him, Paul White, a much more serious character, a mathematician and low-church Christian, and P. I. Dee, for a while my supervisor, who carried apparent omniscience with an engaging charm.

In 1929 Rutherford accepted me as a Ph D student. In those days it was usual for those starting as research students to spend the long vacation working in the 'kindergarten', an institution run by Chadwick. This was supposed to do what the undergraduate practical courses so clearly failed to do, that is, teach the techniques of modern physics. As I was going to study the scattering of slow electrons in gases I was set to learn vacuum techniques by measuring the vapour pressure of tap grease.

It proved a most instructive project and, more important, it enabled me to get to know Chadwick a little. Tap grease was a perennial problem in the Cavendish. It was normally made by a chemist in Southampton named Everett, the son of 'old Everett' who was J. J. Thompson's assistant. Old Everett had been mentioned in an agreement between J. J. and Rutherford, which specified that J. J.'s share of the lab funds would be £150 per annum "out of which he would pay his assistant". This tap grease was made by heating rubber bands with vaseline and adding paraffin wax. As Everett's product was sometimes overcooked and smelt of burnt rubber, the more fussy amongst us made our own. At about this time C. R. Burch, who worked for Metropolitan Vickers, introduced a much superior product prepared by distillation; it was, however, enormously expensive (I think £1 per pot) and in order to get it all of Oliphant's powers of persuasion were needed.

In 1929 I started work in a large room already occupied by Mark Oliphant, Phillip Moon and J. K. Roberts, all of whom were doing experiments involving vacuum techniques. After a few months I was joined by Harrie Massey. The room was just down the corridor from Rutherford's office. He would come round about once a week with Chadwick, and at odd times when he felt like blowing off steam. Once, he came in in the most cheerful good humour and said to Roberts "You know, Roberts, the time has come to consider whether your experiments are worth the liquid air they consume". On another occasion he told me that he never wanted to see me in the lab again. The next morning I got in early and managed to meet him on the stairs; he was particularly friendly. I never really got



Cavendish Laboratory

G. F. C. Searle, Rutherford and Aston



Cavendish Laboratory

Lady Rutherford directing a gang of research students reconstructing her rock garden. The author, in shirt sleeves, looks on. Mr. Lincoln assembled these gangs on days when Rutherford was in London.

to know him well but, as time went on, and particularly after I had left the Cavendish, I found that he would always listen and help me if I needed anything. I remember asking him for help in getting funds to enable one of Townsend's students to leave Oxford and come to work with me. Rutherford's reply was: "Well, I am never averse to any scheme for doing down Prof. Townsend". There was a half humorous resentment between them, dating, I suppose, from the days when they worked together in J. J. Thomson's Cavendish. On another occasion, when Townsend had made a rather intemperate attack on Massey and myself in the Royal Society's Proceedings, Rutherford met me in the corridor and, in great glee, said: "Have you seen what Townsend has said about you? What are you going to do about it". "Nothing," I replied: "Quite right," said Rutherford, "if you answer him he will wait 20 years, but he will get you in the end". It was, I suppose, a totally unjustified view of Townsend but it was enormously encouraging for me; Rutherford had a gift for that sort of thing, he could make you feel a colleague in a great enterprise. His boys were the best boys, surrounded by foolish and wicked men who did not understand what physics was really about. I think he felt himself to be an honest New Zealand farmer's boy fallen into a corrupt society; sometimes that made him rather rude to his more pompous colleagues and rather terrifying to his students. I recently asked Kapitza if he was scared of Rutherford. "Yes", he said; "terrified".

My period in the Cavendish was just before the *annus mirabilis* in which artificial disintegration and the neutron were discovered. Much has been written of this, and it was indeed the source of modern nuclear physics and engineering. My most dramatic memory is of going to the Kapitza Club (a weekly meeting of physicists, usually in Cockcroft's rooms in St Johns) and hearing Chadwick describe the Curie-Joliot results on 'penetrating γ rays', and then going the next week and hearing Chadwick again, explaining that they were really new particles—neutrons—(if he had suspected the truth on the first occasion, he gave no clue).

The fame of these discoveries has obscured the feelings that preceded them. Many young men coming into the subject in the late 1920s felt that it was no time to start to work on radioactivity. The existing techniques had been pushed near their limits and many, including myself, did not realise what could be done with the emerging tech-

nology of electronics. It was Wynn-Williams and Cockcroft who, in different ways, broke the barrier. This involved not only inventing things, but also overturning deep seated traditions of do-it-yourself and not spending money. Cockcroft's elegant solution to the problem of producing 300kV of d.c. power was preceded by some very odd schemes which included using an induction coil given to the University by a collector of scientific equipment, and a Tesla coil (which was noisy enough to produce a complaint from the Master of Corpus, on which Rutherford is said to have commented: "If they don't like the noise why did they build the college there"). An early breakthrough in spending money was the purchase of the doughnut magnet, designed by Cockcroft, which was used to focus α particles. Rutherford, when showing it to a visitor, said: "That cost as much as a research student for a year—but it does twice as much work".

The feeling for economy went all through the organisation; I remember the store man trying to maintain that the existing stock of valves, World War I bright-emitter triodes, must be used up before modern types could be bought. The day-to-day detail was looked after by Mr Lincoln, the fierce head mechanic, whose bark was much worse than his bite. In my third year as an undergraduate I complained about the absence of bandages in the first-aid box, and he said: "What's the use of my keeping bandages, people only come and use them". On another occasion I asked for six inches of one inch steel tube and was surprised when he said: "Certainly I have got just the thing". He went into the room behind the workshop and produced a bicycle left, I suppose by some undergraduate, and told me to saw six inches off the cross bar.

It is easy to tell funny or slightly discreditable stories about the Cavendish in those days, but the fact remains that it was uniquely successful both in discovery and in training many of the most able and effective men of their generation—Blackett, Cockcroft, Kapitza, Oliphant and many others. The defects of parsimony and, to some extent of arrogance, were easily cured in the years that followed. In many ways the experience of the war ideally complemented and compensated for the defects of the training in the Cavendish 10 years before.

For me, Rutherford and Blackett represent most of what is best in physics, and I am deeply conscious of the exceptional advantages that I had from being a student in the right place at just the right time.

(Continued from p. 742)

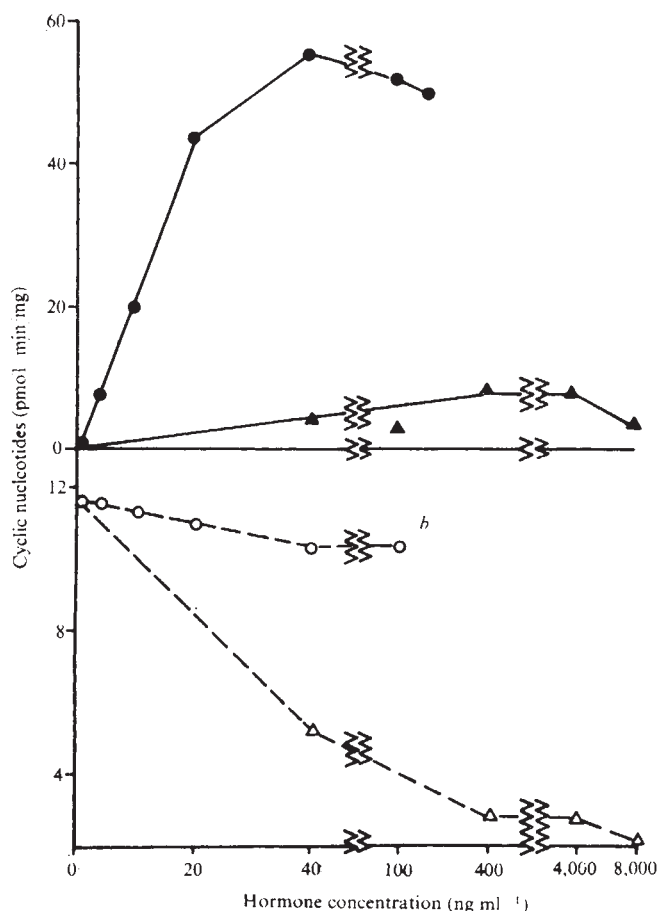


Fig. 3 Changes in membrane-bound cyclase activities. BALB/c 3T3 cells were grown to confluency in 10% serum as in Fig. 1a. After washing and detaching them as in Table 1, and washing further in 0.01 M potassium phosphate (pH 7.4), 0.15 M NaCl, the cells were resuspended in Buffer A (Table 1) and lysed under nitrogen cavitation at 6000 pound inch⁻² in an Artisan Pressure Homogeniser (diameter of orifice 0.068), 5 min being allowed for equilibration. The homogenate was made 0.001 M in EDTA_{Na}, and centrifuged at 2,000 g for 5 min. Plasma membrane fractions were isolated (method to be published). Approximately 2.3 mg of protein was recovered with specific activity for 5'-AMPase of 108 nmol hydrolysed per h per mg protein at 37°C compared with 3 nmol per h per mg in the unfractionated lysate. Reaction mixtures (100 µl) contained for a, guanylyl cyclase (—●—, —▲—): 0.04 M HEPES (pH 7.6), 0.006 M MnCl₂, 0.002 M GTP, 0.0005 M EDTA_{Na}, 0.0005 M DTT, 0.3 M sucrose, 0.01 M theophylline, 0.02 M caffeine, 12 µg of plasma membrane protein, 20 µg BSA or for b, adenyl cyclase (—○—, —△—) 0.006 M MgCl₂ replaced MnCl₂ and 0.002 M ATP, 0.015 M creatine phosphate, 4 µg of creatine phosphokinase replaced GTP. Reactions were incubated for 10 min at 37°C and terminated as described in Table 1. Cyclic nucleotides synthesised were estimated with the radioimmuno assay (Fig. 1). Either varying concentrations of FGF (—●—, —○—) or insulin (—▲—, —△—) were added to incubation mixtures and results are expressed as pmol of cyclic nucleotides synthesised per min per mg of plasma membrane protein, after deduction of the value for a 10 min incubation with no hormone addition for the guanylyl cyclase mixtures (10.5 pmol) or after deduction of the zero time point for the adenyl cyclase mixtures (2.9 pmol). For both reactions synthesis was proportional to time of incubation up to 20 min. Control reactions with added cyclic nucleotides showed no appreciable hydrolysis (less than 2 pmol min⁻¹ mg⁻¹). Boiling FGF for 5 or insulin for 1 h in neutral buffers destroyed their capacity to increase cyclic GMP levels and DNA synthesis in cultured cells and their effects on cyclase enzymes *in vitro*. Addition of 1 µg ml⁻¹ BSA or purified gelatin had no effect on cyclase enzymes *in vitro*.

exogenously-added serum. All these observations strongly implicate cyclic GMP as a positive signal which starts the chain of events leading to the initiation of DNA synthesis and cell division. The apparent transience of the increase in intracellular cyclic GMP does not necessarily negate this, since similar variations are observed in intracellular cyclic AMP concentrations after exposure of cells to adrenergic or peptide hormones whose actions are mediated by cyclic AMP²².

The observed increases in intracellular cyclic GMP concentration and DNA synthesis upon addition of high, non-physiological concentrations of insulin is probably an indirect consequence of additional decreases in intracellular cyclic AMP. Hydrocortisone, as it does not immediately change intracellular cyclic nucleotide levels or activities of the membrane-bound cyclase systems almost certainly exerts its permissive effect through the internal cellular machinery¹³.

The concept of a dualistic theory of cellular control involving cyclic AMP and cyclic GMP both in their antagonistic physiological effects²³ and in control of fibroblast cell growth⁵ may thus be extended to the receptor systems for adenyl and guanylyl cyclase of the plasma membrane and their respective hormones. These systems may possibly initiate cell growth through cyclic GMP or expression of specialised and differentiated functions through cyclic AMP. Though such a general model holds promise not only for physiological events but even more for developmental processes, there are important differences from this relationship. Analysis of cyclic AMP and cyclic GMP concentrations throughout the cell cycle in synchronised fibroblasts show that the specific, transient increase in cyclic GMP occurs early in the G1 phase, whereas cyclic AMP exhibits rhythmic changes during the cell cycle⁵. Results with insulin also stress the possible importance of a negative interference between the two cyclic nucleotide systems. It would not be surprising if growth induction in different organs or tissues in the intact animal were to be primarily controlled by a new class of polypeptide hormones, from the pituitary and submaxillary glands⁹⁻¹¹, which bind to the cell surface and activate the guanylyl cyclase system, the specificity of the inductive process being determined by differences between surface receptors on the various target cells. This could then liberate the adenyl cyclase system for use by those hormones or factors concerned with the synthesis and release of specialised products.

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Evidence for a unique kind of α -type globin chain in early mammalian embryos

MAMMALIAN embryonic haemoglobins are synthesised in nucleated erythroid cells derived from the yolk sac¹. They are structurally different from foetal and adult haemoglobins. It has been generally assumed that the difference of embryonic to foetal or adult haemoglobin is solely due to an embryonic globin chain structurally related to the β chain. It was believed that embryos either synthesise no α -type chain at all or an α chain structurally identical to the adult α chain^{2,3}.

In mice and in rabbits we show the existence of a unique embryonic globin chain (x chain). The different x chains of the two species are closely related in respect to their primary structure and are very similar to the ζ chain of the human haemoglobin Portland 1^{4,5}. The ζ chain can therefore be considered to be a human x-type chain. It was suggested that a haemoglobin found in early human embryos is identical with Portland 1 (refs 6-8).

The presented structural data and the functional relationship of x and α chains prove that the x chains are in fact α -type chains. Furthermore, we find more structural similarities between the x chains of different species than between the x and α chains of the same species. This indicates an early evolutionary divergence of x- and α -chain genes and demonstrates another case of gene duplication of globin genes during evolution⁹.

The embryonic haemoglobins of BALB/c mice and of New Zealand white rabbits were isolated. Embryonic haemoglobins can be separated from adult haemoglobins by column chromatography or acrylamide gel electrophoresis. Using CMC-urea columns, three embryonic haemoglobins are observed in mice: HbE_I, HbE_{II}, HbE_{III}. The tetramer of HbE_I consists of a pair of non- α and a pair of non- β chains: x_2y_2 ; HbE_{II} and HbE_{III} consist of a pair of α and a pair of non- β chains α_2y_2 and α_2z_2 respectively^{10,11}. y and z chains are similar to the β chain and can be regarded as ϵ chains (refs 11-13 and our own observa-

tions, to be published). Using a pH gradient and CMC columns, we found that embryonic haemoglobins of the rabbit consist of at least six haemoglobin fractions: a group of three early eluting embryonic haemoglobins HbE_I-HbE_{III} with the chain composition $x_2\epsilon_2$ plus a group of late eluting embryonic haemoglobins HbL_I-HbL_{III} with the chain composition $\alpha_2\epsilon_2$. There are at least two structurally different ϵ -chains (ref 11 and our results).

Mice and rabbit x chains were separated by chromatography¹⁴⁻¹⁶. In mice the y chain frequently eluted close to the x chain; in rabbits separation between x and ϵ chains is usually incomplete. The x chains were digested by trypsin and the tryptic peptides were separated by the fingerprinting method. The amino acid composition of the tryptic peptides is shown in Table 1. They were compared with α and β chain sequences of mouse, rabbit and carp. According to the principle of least dissimilarity, the best correspondence was obtained using the α chains as a reference. Two peptides of the x chains are identical with typical α -chain peptides (residues 93-99 and 140-141). Several other peptides of the two x chains are similar to α -chain sequences (Table 1, Fig. 1). None of the peptides shows an amino acid composition with closer correspondence to β than to α chain peptides.

Comparing the difference of x and α chains of the same species we found that in the mouse x chain 29 amino acid substitutions are necessary in order to match a sequence of 87 amino acid residues of the α chain. The minimum difference of this stretch is 33%. The difference, if the complete chains are compared, is probably higher, since several x chain peptides are so different from α -chain peptides that they could not be matched at all (Table 1).

In the rabbit x chain we found 24 amino acid substitutions in comparison to a corresponding sequence stretch of 67 amino acid residues of the rabbit α -chain which would reflect a structural difference of 36%. The difference of the human x to the human α chain is in the same order of magnitude with 11 substitutions of a corresponding α chain sequence 38 amino acids long.

Human, mouse and rabbit x chains show much more sequence homology than the x and α chains of the same species. The difference between corresponding peptides with 49 amino acid residues of mouse and rabbit x chains is nine amino acid substitutions, whereas the difference between mouse x and mouse α chain is 19 substitutions. The difference between mouse and human x chains of a sequence of 39 amino acid residues is six substitutions, whereas the difference between mouse x- and mouse α -chain is 13 substitutions. Finally, the difference between rabbit x- and human x-chains is six sub-

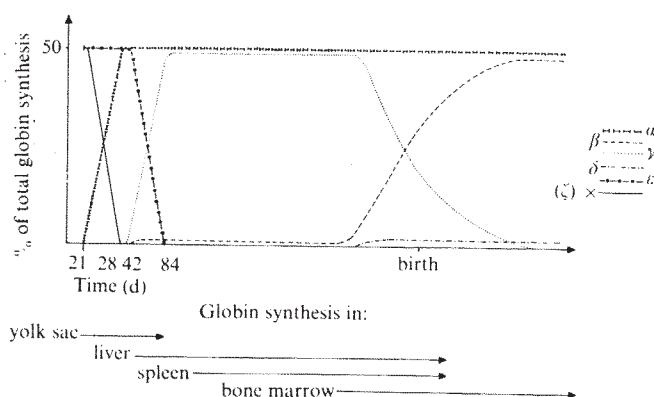


Fig. 1 The amino acid compositions of the tryptic peptides of the human ζ chain and of mouse and rabbit x chains (Tables 1 and 2) were sufficiently similar to some α -chain peptides. The composition data of the human ζ chain were taken from Capp *et al.*⁵. The sequence homologies are shown.

Amino acid pos no	57	61	62	63	63a	70	71	82	83	89	90	92	93	99				
x human	Ala	His	Gly	Ser	Lys			*	Leu	Ser	Glx	Leu	His	Ala	Tyr	Ile	Leu	Arg
x mouse	Ala	His	Gly	Phe	Lys	Val	Met	Val	Asx	Ala	Ile	Thr	Gly	Ala	Lys			
x rabbit	Ala	His	Gly	Thr	Lys	Val	Ala	Val	Asx	Ala	Leu	Ala	Gly	Ala	Lys			
α human	Gly	His	Gly	Lys	Lys	Val	Ala	—	Asp	Ala	Leu	Thr	Asn	Ala	Val	Ala	His	Val
α mouse	Gly	His	Gly	Lys	Lys	Val	Ala	—	Asp	Ala	Leu	Ala	Thr	Ala	Gly	Ala	His	Val
α rabbit	Ala	His	Gly	Lys	Lys	Val	Ser	—	Gln	Ala	Leu	Thr	Lys	Ala	Val	Gly	His	Leu
α carp	Lys	His	Gly	Lys	Lys	Val	Ile	Met	Gly	Ala	Val	Gly	Asp	Ala	Val	Ser	Lys	Ile
Amino acid pos no	32					40				128				139	141			
x human	Leu	Phe	Leu	Ser	His	Pro	Glx	Thr	Lys	Phe	Leu	Ala	Ser	Val	Ser	Thr	Glx	Leu
x mouse	Leu	Phe	Cys	Ser	Tyr	Pro	Glx	Thr	Lys	Phe	Leu	Ala	Ser	Ile	Ser	Thr	Asx	Leu
x rabbit	Leu	Phe	Cys	Ser	His	Pro	Glx	Thr	Lys	Phe	Leu	Leu	Ser	Val	Ser	Thr	Asx	Leu
α human	Met	Phe	Leu	Ser	Phe	Pro	Thr	Thr	Lys	Phe	Leu	Ala	Ser	Val	Ser	Thr	Val	Leu
α mouse	Met	Phe	Ala	Ser	Phe	Pro	Thr	Thr	Lys	Phe	Leu	Ala	Ser	Val	Ser	Thr	Val	Leu
α rabbit	Met	Phe	Leu	Gly	Phe	Pro	Thr	Thr	Lys	Phe	Leu	Ala	Asn	Val	Ser	Thr	Val	Leu
α carp	Met	Leu	Thr	Val	Tyr	Pro	Gln	Thr	Lys	Phe	Phe	Gln	Asn	Leu	Ala	Leu	Ala	Leu

* Lys or Arg

* Lys or Arg

Fig. 2 Scheme of the switches of human haemoglobin chains during ontogenesis. The type of haemoglobin which is synthesised is not organ specific with the possible exception of embryonic haemoglobins. For the time course of erythropoiesis in yolk sac, liver, spleen and bone marrow we used the data cited by Metcalf and Moore¹.

stitutions of a stretch of 39 amino acid residues, the difference between rabbit x and rabbit α chain is 13 amino acids. It is only possible to place a rabbit x-chain peptide into position 71-82 if the insertion of one amino acid in position 63a is accepted. This additional amino acid is also present in the α chain of the carp (Fig. 1).

We also tried to obtain data on the time of synthesis of the embryonic globin chains in the course of embryogenesis. Mouse yolk sac erythropoiesis starts at day 7 of gestation and is succeeded by liver erythropoiesis at day 12-14 (ref 10). It was previously shown that the relative rates of synthesis of the three

embryonic haemoglobins change during the course of embryogenesis. Synthesis of HbE₁ decreases markedly whereas the synthesis of HbE₁₁ increases during embryonic development. The synthesis of HbE₁₁₁ seems to decrease as well¹⁷.

The rate of synthesis of embryonic globin chains was determined by labelling embryonic mouse yolk sac cells at day 9.5 of gestation with ³H-leucine at 37° C for 6 h in leucine-free tissue culture medium, and at day 11.0 with ¹⁴C algae hydrolysate in amino acid free medium¹⁵. Our data show that during the time from day 9.5 to day 11.0 of gestation the rate of synthesis of the ε-type globin chains (y and z) stays constant;

Table 1 Amino acid composition data of the tryptic peptides of mouse and rabbit embryonic x chains

Amino acid	A. Mouse: Residue no. which homologised to known α chain sequences																		Peptides that could not be homologised					
	1-7	17-31	32-40	41-56	57-61	62-70	71-82	83-89	90-92	93-99	128-139	140-141	a	b	a	b	a	b	a	b	a	b	a	b
Lysine	a*	b†	1.4	1	0.9	1.0	1	0.8	1	1.0	1	1.1	0.8	1	1.1	1	1.0	1	0.9	1				
Histidine				3.0	3																			
Arginine		1.0	1	0.8	1				1.0	1														
Aspartic Acid				1.0	1																			
Threonine	1.9	2	1.0	1	0.7	1							0.8	1			1.8	2						
Serine			1.0	1	1.0	1							2.2	2			1.7	2						
Glutamic Acid	4.0	4	1.1	1	2.2	2							2.6	3			1.9	2						
Proline	1.2	1	1.0	1	1.0	1							1.0	1			1.2	1						
Half Cystine			0.5	1																				
Glycine	1.0	1			0.9	1	1.0	1									1.4	1						
Alanine	3.2	3			1.2	1	2.2	2					1.2	1			2.4	2						
Valine							1.8	2									2.0	2						
Methionine	0.8	1					0.8	1																
Isoleucine	0.9	1					0.9	1																
Leucine	0.9	1																						
Tyrosine			0.9	1	0.7	1							0.8	1			3.3	3						
Phenylalanine			1.0	1	2.3	2	0.9	1					2.1	2			1.7	2						
No. of residues yield [10 ⁻⁹ M]	15	43	9	12	16	35	5	27	10	7	29	19	25	12	68	35	8	16	19	10	2	12	4	30
B. Rabbit:																								
Lysine	0.9	1			1.0	1	0.8	1	0.8	1							1.0	1	0.9	1	0.8	1	0.9	1
Histidine					1.4	1																		
Arginine																								
Aspartic Acid	1.0	1																						
Threonine			0.9	1			0.6	1																
Serine			0.9	1					1.0	1	1.0	1												
Glutamic Acid			1.1	1					1.9	2	1.0	1												
Proline			1.0	1					0.4	1														
Half Cystine			§	1																				
Glycine	1.0	1					1.1	1	1.0	1	1.0	1					1.3	1	1.2	1	0.9	1	1.1	1
Alanine	2.3	2					1.1	1	4.5	4	2.2	2					2.3	2	1.7	2	4.0	4	4.2	4
Valine	1.0	1							1.5	2	1.1	1					0.9	1	6.4	6	1.4	1	1.8	2
Methionine																								
Isoleucine																								
Leucine	0.9	1			0.8	1			1.1	1	1.1	1	1.9	2	1.0	1	0.6	1	1.9	2	1.0	1	1.0	1
Tyrosine									0.8	1														
Phenylalanine			0.9	1																				
No. of residues yield [10 ⁻⁹ M]	7	10	8	10	5	8	10	9	12	7	14	3	10	12	6	23	15	6	15	23	9	10	9	12

*a: residues.

†b: nearest whole number of residues.

‡ Phenylalanine is present.

§ Half cystine is usually destroyed during hydrolysis.

|| Proline is present.

The embryonic globin chains of mouse and rabbit were separated as described (11,16). The x chains were digested with trypsin and after separation of the tryptic peptides by fingerprinting the amino acid composition analysis was carried out as described (15). Line 1 indicates the residue numbers that were homologised to known α-chain sequences. The composition data of peptides that could not be homologised to α-chain peptides are also given in the last columns of the Table.

on the other hand the synthesis of the χ chain decreases from 18% to 9% while there is an increase of α -chain synthesis from 82% to 91%. The decrease of χ -chain synthesis is thus compensated by an increase of α -chain synthesis.

Similar data have been obtained for the embryonic haemoglobins of the rabbit. Those haemoglobins which contain χ and ϵ chains (HbE_I-HbE_{III}) show a decrease of the rate of synthesis, whereas those containing α and ϵ chains (HbL_I-HbL_{III}) increase correspondingly during yolk sac differentiation¹¹. These data show that χ - and α -chain synthesis in both species is inversely correlated.

This and the above cited structural evidence proves that the χ chain takes the place of the α chain during early embryogenesis. The χ chain therefore could be expected to compensate for the α chain in situations where no α -chain synthesis is possible. Haemoglobin Portland I tetramer containing $\chi_2\gamma_2$ is observed in infants with homozygous α -thalassaemia^{7,8}.

These data taken together with suggestive evidence of others on the human χ chain⁶⁻⁸ lead us to propose the following scheme of development of globin chain synthesis in man (Fig. 2). As in mice and rabbits we expect, during early yolk sac erythropoiesis, predominantly haemoglobins of the constitution $\chi_2\epsilon_2$. Later, but during yolk sac erythroid differentiation, the α chain replaces the χ chain to give haemoglobins of the constitution $\alpha_2\epsilon_2$. The ϵ chain is replaced by the β chain after the switch of erythropoiesis from the yolk sac to the foetal liver.

In view of this scheme, the existence of ϵ_4 in human foetuses remains unexplained^{2,3}. No ϵ_4 -type haemoglobins have been observed by us during the embryonic phase of erythroid differentiation in mice and rabbits. It might well be that the globin χ chains of the embryonic haemoglobins $\chi_2\epsilon_2$ are degraded at a different rate thus leading to the formation of the ϵ_4 tetramer which is found in human foetuses.

A structural comparison of χ and α chains of mice, rabbits and of man⁵ shows the existence of a group of embryonic χ -type chains which have many features in common. Our data show that the χ -chain genes of all three species have evolved from a common ancestor gene which in turn is derived from an ancestral α -globin gene by gene duplication. We do not know when this duplication occurred, but the many similarities within the three investigated mammalian χ chains and the large common difference as compared to the α -chains suggest that the divergence of α and χ chains is much older than mammalian evolution.

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Hormonal control of oestrogen receptor in uterus and receptivity for ovoimplantation in the rat

THREE distinct states of the rat uterus with respect to ovo-implantation have been described. The prereceptive stage lasting from day 1 to day 4 is followed by receptivity during day 5; finally, during a postreceptive period from day 6 onwards, transferred mature blastocysts do not implant if implantation on day 5 has been prevented¹. Analogous situations can be created in the castrated animal by treatment with a precise sequence of hormones: a minimum of 2 d of progesterone preparation is necessary to obtain, 18 h after the subsequent administration of a small dose of oestrogen the state of receptivity for ovoimplantation which will last for approximately 12 h. Again, a period during which the fertilised egg cannot implant will follow the time of receptivity, as shown by egg transfer experiments¹.

Thus in both intact and castrated animals oestrogen seems to be effective only after progesterone treatment. The possible involvement of the specific high affinity intracellular oestrogen receptor (see papers of the groups of Jensen, Gorski, King, Erdos, Bresciani, Jungblut and this laboratory in ref. 2) in the control of tissue responsiveness for oestrogen has therefore been examined. We have studied the influence of progesterone and oestradiol on the level of oestrogen receptor in both the endometrium and myometrium of the castrated rat uterus. We have compared the results with the variations observed during early pregnancy. There is strong evidence that the presence of such receptors in the cytoplasm is necessary to mediate the action of oestrogen hormones on the target tissues².

We separated uterine endometrium from myometrium by gentle scraping with a scalpel. A Scatchard³ plot was made to show the binding of homogenised endometrium and myometrium supernatant fraction to ³H-oestradiol (as described previously⁴ (Fig. 1). A consistent difference between the apparent equilibrium dissociation constants of the receptor-hormone complexes of the endometrium $K_d = 3 \times 10^{-10} - 5 \times 10^{-10}$ M) and myometrium ($K_d = 6 \times 10^{-10} - 9 \times 10^{-10}$ M) may reflect different degree of interference of low-affinity sites on the binding equilibrium, since straight line Scatchard plots indicating a single class of high-affinity binding sites are obtained when the whole uterus homogenate is used as the source of the supernatant receptor^{2,4}.

The variations in the receptor concentration during pregnancy up to day 8 are shown in Fig. 2. Whether related to total soluble protein or to DNA content of the tissue, the endometrium receptor concentration first decreased

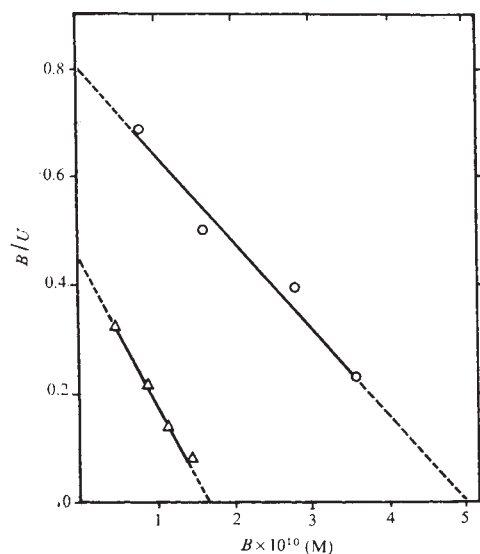


Fig. 1 Determination of the receptor concentration in the endometrium (Δ — Δ) and pooled or individual myometrium ($\circ$ — $\circ$) homogenates. The uterus was removed from a 2 day pregnant rat; the endometrium and myometrium were homogenised separately in respectively 1 ml or 2 ml of the sucrose (0.25 M)— MgCl_2 (3 mM) medium. After low speed centrifugation ($800g \times 10$ min), the supernatant fractions were incubated with radioactive oestradiol for 30 min at 30°C . The receptor bound to unbound (B/U) hormone ratio and the concentration of hormone bound (B) to low-affinity receptor sites in equilibrium solutions (0.2 ml) containing 0.2, 0.5, 1.0 or 2.0 nM ^3H -oestradiol were determined by adsorption with charcoal (0.25% Norit A)-dextran (0.0025%, molecular weight 90,000) suspension (0.5 ml) for 10 min at 30°C (ref. 4). The concentration of the oestrogen receptor binding sites is indicated by the intercept of the experimental straight lines on the abscissa; the inverse slopes of the respective straight lines are equal to the equilibrium dissociation constants ($3.5 \times 10^{-10}\text{M}$ for the endometrium, $6.25 \times 10^{-10}\text{M}$ for the myometrium preparation). Although by this technique only directly available specific binding sites are measured, it has been demonstrated¹⁰ that the concentration of endogenous oestrogen in cytosol is negligible under physiological conditions (oestrus cycle and early pregnancy) when compared to the amount of receptor. The measurement of the receptor concentration in low-speed and in high-speed ($105,000g \times 60$ min) supernatant preparations of rat uterine tissue has been shown to yield identical results¹⁰.

slightly from day 1 to day 2 to rise strongly thereafter. The receptor concentration decreased between days 5 and 8 as seen clearly when expressed on a DNA basis. The values for the myometrium receptor are considerably lower and the variations less marked.

It is known that the secretion of both oestradiol and progesterone in the pregnant rat increases from the evening of day 2 and remains substantially elevated from days 3 to 10 (refs 5,6). Therefore we performed an ovariectomy on the morning of day 2 of pregnancy. We measured the influence of oestrogen and progesterone on the level of oestrogen receptor in the uterus of rats 3 weeks after the ovariectomy. The results are shown in Fig. 2. Both hormones, alone and in combination, caused an increase in the endometrial receptor level. The increase was due partly to cell proliferation but also to a rise in the cellular concentration of the receptor. There was no additivity of oestrogen and progesterone (simultaneously administered) under these experimental conditions. Progesterone showed little effect on the myometrium, whereas oestradiol caused a large increase in the content of myometrium receptor, compared with soluble protein and total DNA. The oestradiol effect on myometrium was significantly counteracted by a simultaneous progesterone administration.

Next we examined the hormone requirements for the maintenance of the elevated endometrium receptor concentration during pregnancy. Rats were castrated on the morning of day 4, and subsequently treated either with progesterone alone or with a combination of progesterone and oestradiol. The receptor concentrations were measured on the following day and compared with these in untreated castrated rats and in intact pregnant controls. We found that neither castration nor the subsequent hormone replacement lead to marked differences in the endometrium receptor level within 24 h. This observation is in agreement with the slow turnover rate of uterine oestrogen receptor (half-life about 5 d) reported by other authors⁷.

In summary, although the presence of oestrogen receptors in the rat endometrium cells may be necessary (maximum levels coinciding with the period of oestrogen sensitivity and implantation), it does not seem to be sufficient to explain the oestrogen effects, since a high level of receptor is found also at stages of pregnancy when oestradiol fails to induce endometrium receptivity for ovoimplantation¹. Progesterone has only been clearly shown to influence the level of

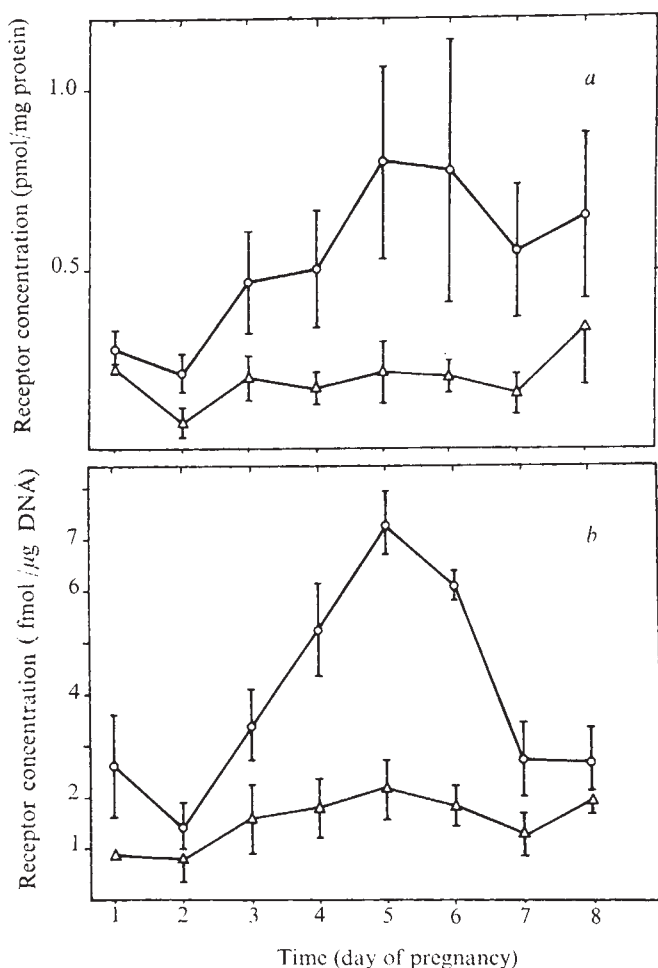


Fig. 2 Endometrium and myometrium oestrogen receptor concentrations in the rat during early pregnancy. The oestrogen receptor concentration in the low speed supernatant preparations was determined as shown in Fig. 1 in endometrium ($\circ$ — $\circ$) or myometrium (Δ — Δ) from individual rates throughout the first 8 d of gestation or in a pool of four myometria (day 1). The results are shown as receptor concentration related to total soluble protein (a) or DNA content (b) of the tissues. Vertical bars show the standard deviations of the mean of at least four determinations.

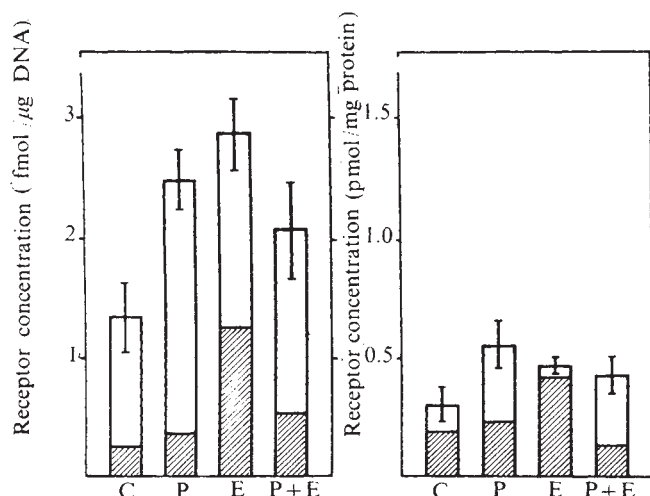


Fig. 3 Effect of progesterone and oestradiol treatment on the endometrium and myometrium oestrogen receptor concentrations in castrated rats. The concentration of oestrogen binding sites in the low speed supernatant preparation was determined as shown in Fig. 1 in endometrium of individual rats (whole bars) or in pooled myometrium (shaded part of the bars, four rats per determination). The rats received subcutaneously: the vehicle (propylene glycol) alone (control, C), progesterone (P, 5 mg per injection), oestradiol (E, 0.25 μ g per injection) or both hormones (P+E). The treatment was repeated twice with an interval of 24 h and the animals were killed 24 h after the second injection. The vertical lines represent standard deviation of the mean (four determinations).

oestradiol receptors in the endometrium, the changes in the myometrium being disputable. This, together with the lack of systematic study, may account for the fact that the progesterone effect on the uterine oestrogen receptor has escaped earlier detection. Whether the progesterone effect on oestrogen receptor is realised through the stimulation of receptor synthesis or activation in all or only certain cells, or through the preferential stimulation of mitotic activity of oestrogen-responsive cells, remains to be explored.

Perhaps of even greater interest is the antagonistic effect of progesterone in the oestradiol stimulation of the oestrogen receptor level in the myometrium. The observed variations in the receptor concentration in the endometrium and myometrium between days 2 and 5 of gestation can best be interpreted by simultaneous action of the two hormones. There is therefore a possibility that by blocking the increase of oestrogen receptor level in the myometrium, progesterone inhibits the excitatory action of oestradiol⁸ and thus favours implantation. This negative aspect of progesterone action could be as important as the increase of the endometrium oestrogen receptor which it provokes. A study of changes in the progesterone receptor has recently been published⁹. This work provides another model system where the antagonistic and synergistic effects of oestradiol and progesterone may be studied at a molecular level.

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Methylmercury is a potent inhibitor of membrane adenylyl cyclase

THE toxicity of methylmercury has taken on added importance since it was discovered that inorganic mercury can be converted to methylmercury by bacteria in bottom sediments of lakes and homogenates of rotting fish^{1,2}. The mechanism for methylation of inorganic mercury by bacteria has been described in some detail^{3,4}. Although there have been several documented incidents involving the toxicity of alkylmercury derivatives⁵⁻⁷, the basis for methylmercury toxicity has not been defined unambiguously. One possible target site for methylmercury—the plasma membrane—is described in this communication.

Many macromolecules in mammalian cells could be modified chemically by methylmercury. In principle, any enzyme with an essential sulphhydryl group is a potential target for methylmercury. However, components of the plasma membrane must be given primary consideration since methylmercury is lipid-soluble⁸ and the plasma membrane is the cellular organelle most vulnerable to external agents. An examination of central nerve tissue from victims of the Minamata disaster in Japan revealed considerable morphological damage to plasma membranes⁹ and methylmercury has been reported to catalyse the hydration and hydrolysis of plasmalogens, when the reaction was examined in methylene chloride¹⁰. Alternatively, it is important to determine whether or not functional proteins in plasma membranes are sensitive to methylmercury. Crucial membrane activities known to be inhibited by sulphhydryl reagents include adenosine triphosphatases, acetylcholine esterase, adenylyl cyclase, transport systems, depolarisation phenomena in nerve and muscle tissue and hormone binding¹¹. We have now found that methylmercury is a potent inhibitor of adenylyl cyclase in rat liver plasma membranes.

Table 1 Inhibition of membrane adenylyl cyclase by sulphhydryl reagents

Sulphydryl reagents	*Concentration for 50% inhibition (M)
Iodoacetic acid	3×10^{-3}
Iodoacetamide	3×10^{-3}
N-ethylmaleimide	$\sim 1 \times 10^{-3} \ddagger$
p-CMB	$5 \times 10^{-4} \ddagger$
p-Chloromercuriphenyl sulphonate	$4 \times 10^{-6} \ddagger$
5-Bromo-5-phenyl-barbiturate	6×10^{-6}
Mercuric chloride	$\sim 1 \times 10^{-6}$
Methylmercury chloride	1×10^{-7}

* Rat liver membranes incubated for 15 min at 30° C with the sulphhydryl reagent.

† Rat liver membranes incubated at 22° C for 15 min¹⁵.

‡ Heart muscle adenylyl cyclase at 37° C (ref. 16).

Methylmercury chloride was synthesised by the method of Imura *et al.*¹². Purity was verified by thin-layer silica gel chromatography developed with diethyl ether: petroleum ether (3:7). The concentration of aqueous solutions of methylmercury chloride was quantitated using a Coleman mercury analyser. Rat liver plasma membranes were prepared by the Neville procedure as modified by Rodbell¹³ and adenyl cyclase was assayed by the Krishna technique¹⁴. The final assay media contained 25 mM Tris, pH 7.6, 1 mM EDTA, 5 mM MgCl₂, 5 mM theophylline, 15 mM NaF, 1 mM ³H-ATP (2.5 μ Ci), 2 mM cyclic AMP, 20 mM creatine phosphate, 1 mg ml⁻¹ creatine kinase and 0.1% bovine serum albumin. Membranes were treated with methylmercury chloride by incubating a sample (80 μ g protein) with 200 μ l of 0.01 M phosphate buffer, pH 7.00, containing various amounts of methylmercury chloride. After 15 min of incubation, 5 ml of phosphate buffer was added and membranes were centrifuged at 20,000g for 10 min at 4° C. The pellet was dispersed carefully in buffer using a 20 gauge hypodermic needle and assayed in quadruplet for NaF stimulated adenyl cyclase activity. Enzyme activity is expressed relative to the control which consisted of membranes treated as described above with buffer containing no methylmercury chloride. The control membranes catalysed the formation of 1.00 nmol cyclic AMP per mg protein per 10 min in the presence of NaF.

Adenyl cyclase activity in rat liver plasma membranes proved to be extremely sensitive to methylmercury chloride (Fig. 1). Concentrations of methylmercury chloride as low as 10⁻⁸ to 10⁻⁹ M partially inhibited enzyme activity. Fifty per cent inhibition occurred at 1 $\times$ 10⁻⁷ M when incubation was carried out at 30° C for 15 min. This inhibition was not due to inhibition of the ATP regenerating system in the assay since the membranes treated with methylmercury were washed thoroughly before assaying for adenyl

cyclase activity, and creatine kinase would have been in excess of methylmercury even without washing. It is interesting that when membranes were incubated with methylmercury at 4° C adenyl cyclase was not inhibited. It is possible that inhibition of membrane adenyl cyclase activity requires diffusion of the inhibitor through the membrane phase, which could be reduced drastically below the thermal transition point of the lipids. Inhibition by methylmercury at 30° C was reversed by mercaptoethanol but only 80% of the original activity could be restored.

The effectiveness of methylmercury as an inhibitor of adenyl cyclase is compared with several other sulphhydryl reagents in Table 1. Methylmercury is the most potent inhibitor of adenyl cyclase reported so far. Two properties of methylmercury probably account for this: first, organomercurials generally react quite rapidly with protein sulphhydryl groups; secondly, methylmercury is quite lipid-soluble and would be expected to concentrate in the membrane phase when distributed between an aqueous phase and membranes.

The molecular basis for methylmercury toxicity is not known and there may of course be multiple effects. But, any consideration of alkylmercury toxicity must take into account the sensitivity of adenyl cyclase to methylmercury and the pivotal role this enzyme plays in the metabolism of mammalian cells.

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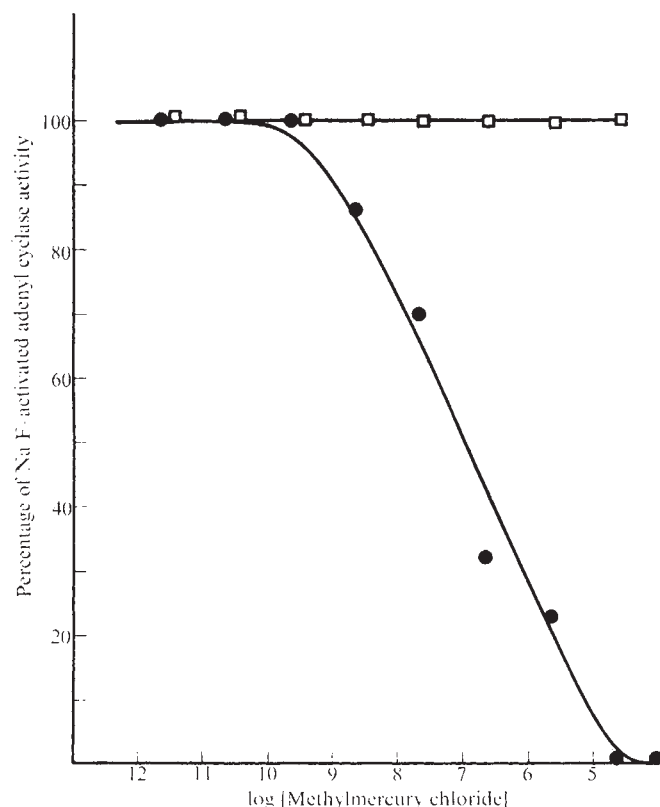


Fig. 1 Concentration dependence for methylmercury inhibition of adenyl cyclase. Rat liver plasma membranes were incubated with various concentrations of methylmercury chloride for 15 min at 30° C (●) or 4° C (□). After incubation, the membranes were assayed for NaF-stimulated adenyl cyclase activity as described in the text.

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Effects of thyroid state on adrenoceptor properties

RECENT studies with frog hearts have shown that the adrenoceptors that mediate inotropic responses are altered qualitatively by ambient temperature¹⁻³. The characteristics of these receptors changed from β to α when the temperature of the isolated hearts was reduced through a critical range of 17°–22° C, which suggested that α and β adreno-

Table 1 Effect of altered thyroid state on the sensitivity of rat left atria to adrenergic agonists

	Control	<i>P</i>	Thyroidectomised	<i>P</i>	Thyroidectomised + T ₃ or T ₄
Isoproterenol	8.83 ± 0.16* (10)	< 0.005	7.81 ± 0.19 (13)	< 0.005	9.45 ± 0.21 (6)
Noradrenaline	7.12 ± 0.09 (30)	< 0.005	6.20 ± 0.04 (40)	< 0.005	7.27 ± 0.14 (13)
Phenylephrine	5.45 ± 0.09 (20)	< 0.05	5.74 ± 0.10 (32)	< 0.05	5.38 ± 0.11 (8)

* Mean + s.e., error of pD_2 (negative logarithm of molar concentration required to produce half-maximal response). Numbers of experiments are given in parentheses. *P* values indicate significance of differences between adjacent groups.

ceptors represent allosteric conformations of the same structure³. Although a change in adrenoceptor characteristics qualitatively similar to that found in the frog heart seems to occur in the mammalian myocardium^{1,4,5}, the physiological significance of a temperature-induced change is obviously limited in homeothermic species. But, several observations indicate that conditions which promote α -adrenoceptor properties, including cold¹⁻³, iodoacetate or fluoroacetate⁶ or dinitrophenol¹, inactivity of skeletal muscle⁷ and increased vagal influence on the myocardium⁸, are associated with a decrease in metabolic activity. Therefore, it seemed possible that hypothyroidism would produce similar changes in receptor properties. We report here that the characteristics of adrenoceptors mediating inotropic responses in hypothyroid rats are similar to those in normal hearts at low temperatures.

Hypothyroidism was induced in male Sprague-Dawley rats (180–220 g) by surgical thyroidectomy. Experiments were performed on isolated left atria 6–10 weeks after the operation. By this time growth was retarded and the fur was dry. Serum thyroxin levels determined by the competitive protein binding assay⁹ were significantly lower (25 ± 4 ng ml⁻¹) than those of control animals (57 ± 6 ng ml⁻¹). Control preparations were from either sham-operated age-matched, or weight-matched animals. The results from the two control groups were almost identical and were pooled. A third group consisted of thyroidectomised rats injected daily with thyroxine (T₄, 1.0 mg kg⁻¹) or triiodothyronine (T₃, 0.25 mg kg⁻¹) for 1 week before use. The animals were anaesthetised with ether and the hearts were removed immediately. The left atria were suspended in Krebs-Henseleit solution at 31° C bubbled with 5% CO₂ in O₂, and were stimulated through platinum electrodes with square-wave pulses at a voltage slightly above threshold, a duration of 3 ms and a rate of 1 Hz. Isometric contractions were recorded by a force-displacement transducer and Grass polygraph. Cumulative concentration-response curves for various agonists were determined before and after a 40 min incubation with propranolol (0.04–4.0 μ M) or ³H-phenoxybenzamine (³H-POB, specific activity 33 mCi mmol⁻¹, 7.3 μ M). Responses are expressed as percentage of the maximal control response. Atria exposed to ³H-POB were washed for 2 h and then dismantled and freeze dried. The dry tissue was weighed and dissolved in NCS tissue solubiliser; radioactivity was measured in a liquid scintillation counter. The retained radioactivity is expressed as d.p.m. per mg dry weight.

Thyroidectomy did not significantly alter either the basal contractile force of left atria or the maximal increase in force produced by the sympathomimetics tested. But, selective changes in sensitivity to the various amines were re-

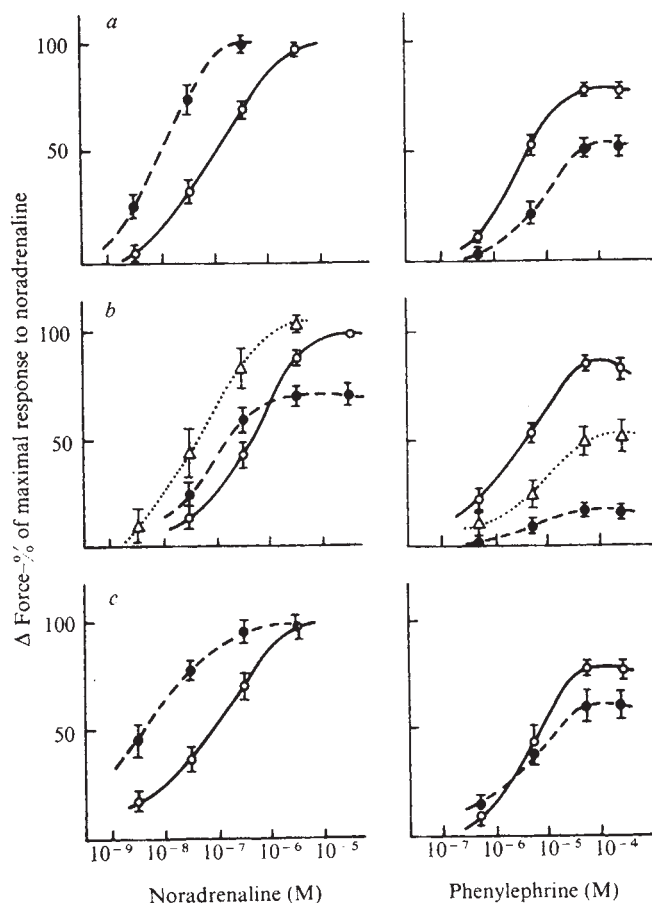


Fig. 1 Effects of phenoxybenzamine on inotropic responses of rat left atria to noradrenaline and phenylephrine. Rats were normal (a), thyroidectomised (b); and thyroidectomised + T₃ or T₄ (c). ○, Control responses; ●, after exposure to phenoxybenzamine (7.3 μ M); △, after exposure to phenoxybenzamine (7.3 μ M) in the presence of phentolamine (26.5 μ M). Means $\pm$ s.e. are shown.

Table 2 Effect of altered thyroid state on the inhibitory potency of propranolol

Propranolol (μ M)	Control	<i>P</i>	Thyroidectomised	<i>P</i>	Thyroidectomised + T ₃ or T ₄
0.04	0.70 ± 0.09* (11)	< 0.05	0.37 ± 0.07 (7)	< 0.05	0.75 ± 0.10 (5)
0.4	1.84 ± 0.15 (11)	< 0.005	0.70 ± 0.10 (8)	< 0.005	1.70 ± 0.21 (5)
4.0	3.01 ± 0.37 (5)	< 0.005	1.39 ± 0.07 (8)	< 0.005	2.54 ± 0.38 (5)

* Mean + s.e. of log dose-ratio (logarithm of the ratio of NA ED₅₀s after and before propranolol). Numbers of experiments are given in parentheses. *P* values indicate significance of differences between adjacent groups.

flected in significant changes in the concentrations producing half-maximal responses. Table 1 shows that the sensitivity of atria to isoproterenol and noradrenaline, agonists with predominantly β -adrenoceptor activity in the heart, was significantly lower, whereas sensitivity to the α -adrenoceptor agonist phenylephrine was significantly higher in the thyroidectomised than in the control rats. Sensitivities to all three agonists were returned to or beyond the control values in the thyroidectomised animals treated with thyroid hormone. There were also reciprocal changes in the effectiveness of α and β -adrenoceptor antagonists. The inhibitory potency of propranolol was at least ten times less in the thyroidectomised than in either the control or the thyroidectomised, hormone-treated groups (Table 2). Conversely, POB inhibited inotropic responses more effectively in hypothyroid than in the other groups (Fig. 1). In control atria POB potentiated inotropic responses to noradrenaline and moderately inhibited those to phenylephrine. In preparations from thyroidectomised rats a similar exposure to POB partially inhibited responses to noradrenaline and blocked those to phenylephrine significantly more than in the controls. Maximal responses of these preparations to CaCl_2 were unaltered by POB. Thyroid hormone treatment reduced the effectiveness of POB on responses to both noradrenaline and phenylephrine to about the control level. In association with the increased blockade, significantly more ^3H -POB was bound to the hypothyroid myocardium ($25,122 \pm 1,365$ d.p.m. ml^{-1} dry weight) than to preparations from either control ($19,310 \pm 1,176$) or thyroidectomised, hormone-treated rats ($16,384 \pm 857$). When atria from thyroidectomised rats were exposed to ^3H -POB in the presence of $26.5 \mu\text{M}$ phentolamine, protection of α adrenoceptors was shown by a significant reduction in both the blocking effectiveness (Fig. 1, dotted lines) and the binding of ^3H -POB ($18,212 \pm 1,190$). These data indicate the presence in hearts from hypothyroid rats of α adrenoceptors that are absent or are unreactive with POB in euthyroid animals. They also suggest that, as in frog hearts at low temperatures³, α adrenoceptors represent a considerably higher percentage of the total binding sites for POB in hypothyroid myocardium than in normal vascular smooth muscle¹⁰.

The observed shift in the balance of α and β adrenoceptors involved in inotropic responses can be interpreted either as due to reciprocal changes in the sensitivity or availability of two independent pools of receptors, or to a single type of adrenoceptor that is qualitatively altered by changes in thyroid state. The experiments reported here do not distinguish between these possibilities. But, analogies between this model and temperature-induced receptor transformation, where the second interpretation was supported by the observation that β adrenoceptors did not appear at high temperatures after α adrenoceptors had been alkylated irreversibly at a low temperature³, suggest that the changes in responsiveness produced by altered thyroid hormone levels reflect an interconversion of myocardial α and β adrenoceptors. In view of the reported sensitivity of allosteric systems to thyroid hormones^{11,12}, this interconversion can be envisaged as an allosteric change in a single basic type of adrenoceptor, as proposed earlier³.

Such a change in adrenoceptor characteristics due to altered thyroid hormone levels could explain several published observations, including a decreased blocking potency of propranolol in the hearts of hypothyroid rats¹³, a selective increase in adrenergic stimulation of the aorta of hypothyroid rabbits¹⁴, a diminished lyipolytic response to noradrenaline in adipose tissue from hypothyroid human subjects¹⁵, a decreased adrenergic vasoconstriction, reversed by pronethalol, in the hind limbs of hyperthyroid dogs¹⁶, and an increased sensitivity to phenylephrine and decreased sensitivity to isoproterenol of atria from propylthiouracil-pretreated rats^{17,18}.

Although both α and β adrenoceptors can mediate posi-

tive inotropic responses in the mammalian myocardium¹⁹, the underlying mechanisms may differ. It has been reported that stimulation of α adrenoceptors is not associated with an 'oxygen-wasting' effect²⁰, and is not accompanied by increased accumulation of cyclic AMP²¹. It is therefore tempting to speculate that changes in adrenoceptor characteristics play a role in the adaptation of mechanical responses of the myocardium to its metabolic state.

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Stereopsis in dynamic visual noise

A NOISE signal has the useful property that convolution of the output spectrum with the reciprocal of the input spectrum gives a measure of the characteristics of the transmitting system. In visual perception it is not possible to obtain the output spectrum directly, but an observer can report on features of the 'perceptual output' of the visual system¹. One striking characteristic which may be observed is the generation of stereoscopic depth merely by an interocular delay in transmitting binocular dynamic visual noise.

Ross² has recently described the effects of an interocular delay in perception of random dynamic noise (an electronic snowstorm) generated by a sophisticated computer technique. He interpreted his results as showing that a temporal rather than disparity between the two eyes may act as a signal for stereoscopic depth. The concept of stereopsis from temporal disparity is a radical one and needs to be critically examined before being fully accepted. I shall describe some observations and a theoretical viewpoint which seems to provide an explanation for dynamic noise stereopsis within the framework of stereopsis from spatial disparity.

The display used for the observations consisted of

random visual noise generated by a detuned television receiver. An interocular delay of up to 100 ms may be produced by the classic technique of a neutral density filter in front of one eye³. Observation of the dynamic noise with a one log unit filter (creating a delay of about 30 ms at 10 trolands when fully adapted³) gave rise to a number of perceptual experiences which have been spontaneously confirmed by six observers. The noise exhibits a considerable depth, perhaps 10% of the viewing distance, and also a streaming motion which is leftwards in front of the point of fixation and rightwards behind fixation with the filter over the left eye. Direction of movement reverses with the filter over the right eye. The motion had the characteristics of motion in a landscape viewed from a moving train, such that points near fixation rotated slowly whereas points well in front of or behind fixation moved more quickly. Movement is leftwards in front of fixation with the filter over the left eye. Direction of movement reverses if the filter is switched to the right eye.

The range of interocular delays for depth probably depends on the density and spatial distribution of the dynamic noise. In my display depth could be perceived with as little as 5 ms delay and as much as 70 ms, the maximum obtainable. One interesting observation was that depth and in particular movement were enhanced by tracking the movement of one depth plane across the screen. Tracking also seems to enhance the unity and salience of the plane which is being tracked. In contrast tracking the conventional Pulfrich pendulum against a plain background has the effect of abolishing depth.

As a control for any peculiarities of the television noise which may have influenced the results, observers tilted their heads from vertical to horizontal. The scan rate in the transverse plane through the two eyes changes from 64 μ s to 40 ms between vertical and horizontal. The plane of movement rotates to remain parallel to the two eyes,

and otherwise no change in the percepts described was reported.

These observations confirm that stereopsis may be obtained by interocular delay in viewing random noise. In this situation there is no correlation between the signals from the two eyes at any instant in time. It is therefore difficult to understand what can give rise to a perception of a range of disparities in the stimulus. The model I propose is based on the assumption that the two percepts of depth and movement arise from the same operation on the dynamic noise stimulus. Thus Ross's hypothesis of depth produced by temporal disparity also implies that movement can be produced by temporal differences alone, whereas logically movement involves both temporal and spatial displacement. To resolve this difficulty, I considered the microstructure of the dynamic noise, rather than regarding it as random and therefore unpatterned. Figure 1 shows how depth and movement both arise from chance associations of points at different times in the random display. The single postulate of an association between depth and movement arising from the same pair of points is all that is required to produce the percept of a rightward-moving spot behind the plane of fixation. Such an association between the monocular movement and binocular depth is not unlikely since stationary monocular stimuli tend to be drawn to a stereoscopically defined depth⁴.

It is difficult to reconcile Ross's description of a single depth plane with the dense range of depths reported by my observers.

Preliminary observations of my dynamic noise stimulus with a dark central square confirm that depth is now perceived predominantly to the rear of the plane of the card. This may be due both to gestalt figural organisation favouring an underlying as against overlying interrupted surface, and to the difficulty of making tracking eye movements with the square present.

My observations support the hypothesis that an interocular delay produces a random distribution of spatial disparities in a dynamic noise stimulus. Each disparity is associated with a certain rate of apparent movement, giving rise to the perception of moving depth planes. The observations may thus be accommodated within the conventional framework of stereoscopic theory.

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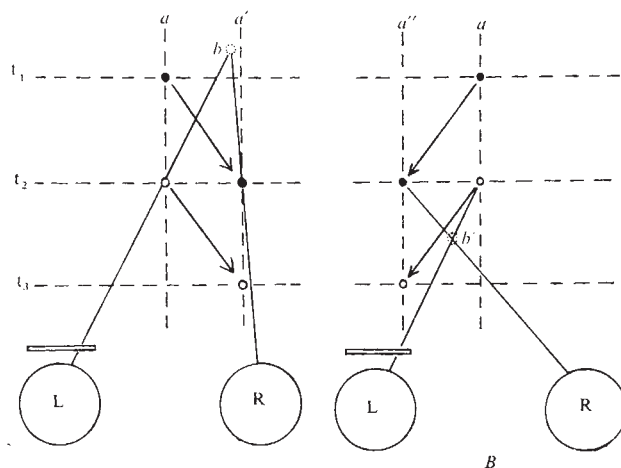


Fig. 1 *A*, Sequence of possible events at three points in time. Left and right eyes are depicted as viewing events only at t_2 . A spot at point a is transmitted by the right eye (●) at time t_1 . As a result of the interocular delay the same spot is transmitted to the left eye at time t_2 (○). If a second spot happens to appear at a' to the right of a such as to be transmitted at time t_2 , a spatial disparity is produced and a spot will be perceived in a different depth plane at b . The monocular sequences of a spot at $a(t_1)$ followed by a spot at $a(t_2)$, and a spot at $a'(t_2)$ followed by one at $a'(t_3)$ are both preconditions for monocular apparent movement to the right, which may therefore be associated with the spot at depth b . *B*, reversal of both depth and movement when the second spot appears to the left of a at a'' rather than the right. In a random display both sequences *A* and *B* will occur, producing both rightward movement behind the point of fixation and leftward movement in front. The distances from a to a' and a to a'' will vary with a Poisson distribution depending on the density of the visual noise.

Contractility in *Spirostomum* provides for nonelectrogenic calcium regulation through energy-dissipative metabolic processes in the absence of membrane excitability

ATTEMPTS to carry out *in vivo* pharmacological analyses of the events leading to contraction in fast acting muscle systems have been hampered by problems due to, for example, intracellular diffusion, cell-cell interactions and extracellular control mechanisms, which arise in part because of the multicellular organisation of many vertebrate muscle systems. Their effect is to impede accurate measurement of rapid changes in the physiological and ultrastructural states throughout the system in response to

specific stimuli. The most troublesome aspects of these problems can be bypassed through the use of single-celled models which have the same properties of excitability as do muscle systems.

An essential feature of contraction in the ciliated protozoan *Spirostomum*, as in muscle, is the requirement for calcium to couple stimulation and contraction. There is a temporal relationship between calcium release into the cytoplasm and the onset of contraction in cells micro-injected with the calcium-sensitive, bioluminescent protein aequorin¹. In spite of the similarity in calcium dependency, systems such as *Spirostomum* and muscle differ in the ultra-structural organisation and energy requirements of their contractile apparatus²⁻⁴. In addition, *Spirostomum* responds to many chemical and physical stimuli in the absence of recordable changes in the electrical properties of the cell membrane¹. The response is a very specific set of contractions and provides a means of examining the biochemical pathways which may regulate calcium release during pharmacomechanical stimulation.

Dikstein⁵ suggested that several redox systems in cells are in such tight equilibrium with redox substrates and

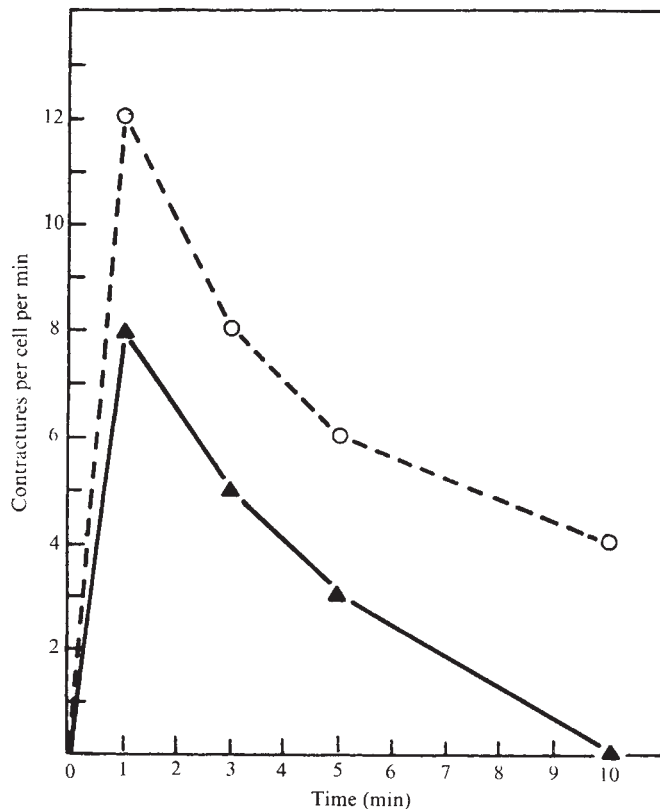


Fig. 1 Time of course and magnitude of the contractile responses of *Spirostomum* to treatment with 10^{-4} M (O) and 10^{-3} (Δ) PMS.

products as to affect ATPase activity, energy coupling and excitation. Such regulation of metabolic activity can be studied by varying the redox ratio $\text{NADPH} : \text{NADP}^+$ (and $\text{NADH} : \text{NAD}^+$ ratio through transhydrogenation). Some NADPH is generated during the biosynthesis of pentose monophosphates, and it functions as a reducing equivalent in the biosynthesis of fatty acids, steroids and certain purines. Some of the reducing equivalents from NADP are oxidised through the microsomal respiratory chain mediated by cytochrome P-450 and atmospheric oxygen as part of the hydration of toxic substances⁶. The availability of NADPH can be controlled by an intermediate hydrogen carrier, phenazine methosulphate (PMS),

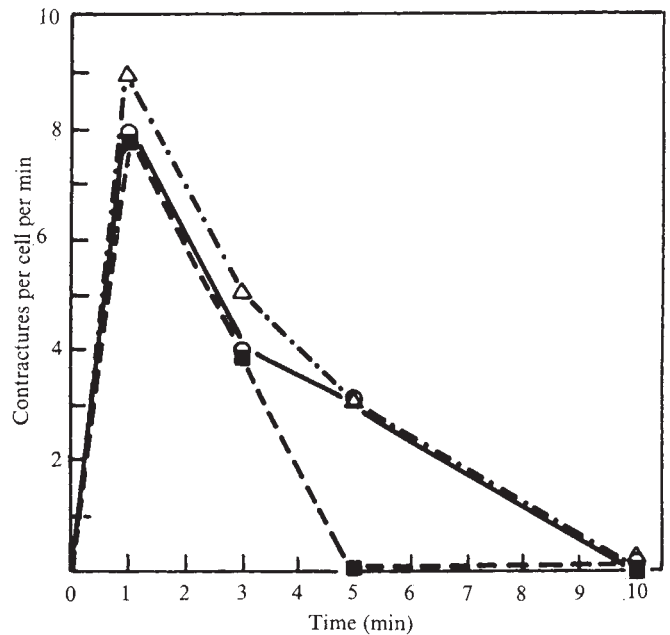


Fig. 2 Influence of PMS on cells depolarised in high KCl medium. The most significant effect occurs at 40 mM KCl when there is a 33% decrease in the maximum number of contractions exhibited by the cell under conditions of maximal stimulation. Concentrations of KCl: O, 10 mM; Δ, 20 mM; ■, 40 mM.

which accepts hydrogen from NADPH (and NADH) and transmits it to a suitable oxidising agent such as neotetrazolium or oxygen. This generates an energy sink and deprives mitochondria of reduced substrates.

When we treated *Spirostomum* with 10^{-4} M and 10^{-3} M PMS in a medium consisting of 2 mM NaCl; 0.5 mM KCl; 0.05 mM CaCl_2 ; 0.1 mM KH_2PO_4 , and 0.1 mM KOH (pH 6.3) contractions were induced in each cell (Fig. 1). Data were tabulated according to the method of Sleigh⁷ who counted contractions per minute for several cells at regular intervals as a direct assay of their behavioural responses to pharmacomechanical stimuli. At the higher concentration of PMS each cell made a maximum

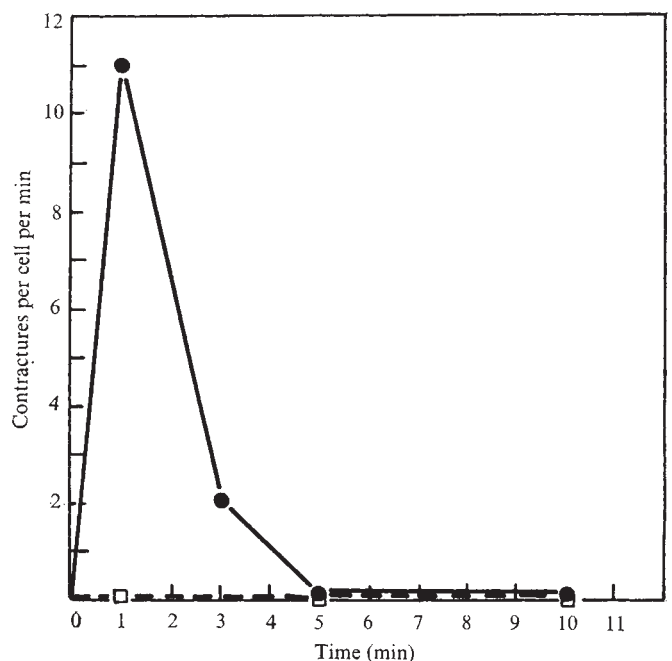


Fig. 3 Net effect of the calcium ionophore A-23187 at 10^{-3} M (●). Total inhibition of PMS induced contractions occurs in calcium-free Chalkey's medium (□).

of twelve contractures per minute during the first minute of stimulation, followed by a slower exponential decay at a rate of two contractures per minute until contraction stopped within 30 min. Further treatment with PMS did not elicit further contractures. To insure that PMS was not initiating contractures by depolarising the cell membrane, the concentration of KCl in the medium was adjusted at 10 mM, 20 mM and 40 mM to depolarise the membrane before treatment. Figure 2 shows that a maximum of 33% depression of 10^{-4} M PMS-stimulated contractures occurred when cells were preincubated in 40 mM KCl.

At the cessation of PMS-induced contractures, the terminal vacuole of the cell enlarged, occupying a third to a half of the cell volume. This indicated that the osmotic activity of the vacuolar space increased, possibly due to the sequestration of Ca^{2+} during relaxation after PMS-induced contractures. Vacuolar calcium concentration has been reported⁸ to increase after repeated mechanical and electrical stimulation of *Spirostomum*, suggesting that PMS action is metabolically linked to cyclical calcium movements in the cellular compartments. To test this hypothesis, the calcium ionophore A-23187 (Eli-Lilly) was added to calcium-free and complete medium in a concentration 10^{-5} M for 10 min before stimulation with PMS. Preincubation did not affect the ciliary locomotory activity. As Fig. 3 shows, in the presence of 0.05 mM Ca^{2+} the cell still made the maximum number of contractures, but these decayed at two to three times the initial rate going to baseline in 5 min. In calcium-free medium, preincubation in A-23187 followed by PMS stimulation produced a single contraction from which the organisms failed to recover. These results suggest that the cell accumulates calcium from the medium, as Jones⁹ suggested, which would then be available for activation. Pautard¹⁰ indicated that some membrane-limited calcium is bound tightly in the form of hydroxyapatite in *Spirostomum*. Our results might also indicate the slow chelation of stored calcium by the ionophore and subsequent free diffusion of the ion away from sites of calcium storage and release. The terminal vacuole failed to enlarge

during treatment with the ionophore and PMS, indicating that calcium was being removed through chelation with the ionophore, which then prevented calcium sequestration.

Figure 4 shows the effect of chlorpromazine and dicyclohexyl carbodiimide (DCCD), which Maran *et al.*¹¹ reported to inhibit PMS activation of *Vorticella*. Both substances inhibit enzymatic reactions which involve transfers of inorganic phosphate. Our results indicate that DCCD eliminated PMS induced contractures and elicited no further responses. Chlorpromazine depressed the PMS response. This drug, however, showed some delayed activity of its own, independently inducing contractures between 3 and 5 min after application.

Our results support the concept that calcium movements, and hence contractility, can be influenced directly by changes in the metabolic state of a contractile cell apparently independently of any alteration in the external concentration of ions governing the electrical properties of the membrane or of contractility. Storage of Ca^{2+} within cellular compartments against its electrochemical gradient represents a source of chemical potential energy. Presumably, the release or efflux of calcium can be coupled to the synthesis of energy-rich intermediates which may be used for resequestration and for the active processes involved in contraction¹². Ultimately in *Spirostomum*, such a system would run down because the energy available to re-establish a calcium chemical potential is continually depleted in the presence of PMS by other active processes within the cell. We suggest that motile or contractile processes such as dividing cells, amoeboid movement, cytoplasmic streaming and other processes with an implied calcium dependency, may well depend on local changes in metabolism which in turn regulate the amount of free calcium within various cytoplasmic compartments.

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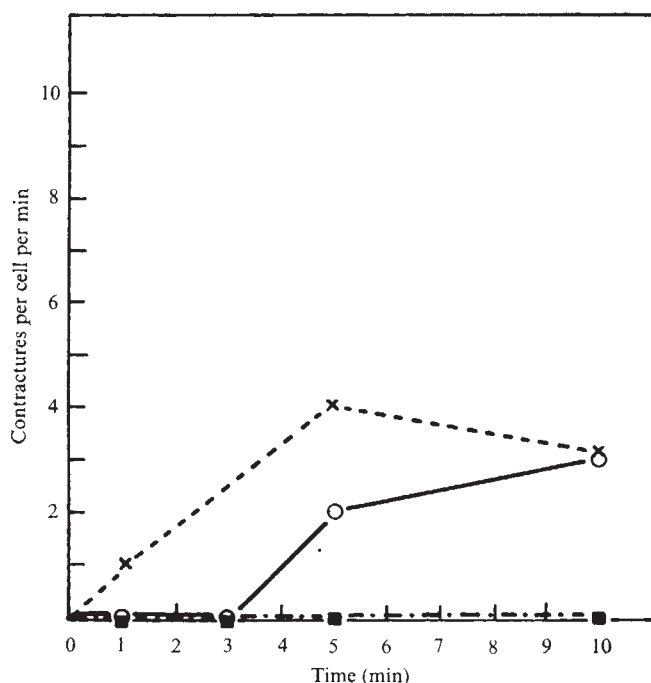


Fig. 4 Chlorpromazine depresses the response to PMS and acts as a delayed independent stimulus. Dicyclohexyl carbodiimide (DCCD) inhibits PMS-induced contractures by blocking PO_4 transfer reactions. $\times$, 10^{-5} M chlorpromazine as inhibitor of PMS; O , 10^{-5} M chlorpromazine as stimulus; $\square$, 10^{-5} M DCCD, before and after PMS.

Inhibition of interferon action by plant lectins

IN spite of various theories, the mechanism of the antiviral action of interferon¹⁻³ remains obscure. Previous work indicated that it does not have to penetrate into target cells to exert its effect. Mouse interferon preparations, when covalently

Table 1 Effect of lectins on antiviral activity of Sepharose-bound interferon

Addition to cell monolayer	Lectin pretreatment of beads cells		Viral yield after pretreatment with			
			PHA	Con A	Lotus lectin	Orange lectin
Control Sepharose	—	—	4,096	4,096	4,096 (8,192)	2,048
Control Sepharose	+	—	4,096	4,096	4,096 (4,096)	Not done
Control Sepharose	—	+	4,096	2,048	4,096 (4,096)	Not done
Control Sepharose	+	+	4,096	4,096	4,096 (8,192)	2,048
IF-Sepharose	—	—	32	64	32 (64)	64
IF-Sepharose	+	—	128	4,096	512 (2,048)	Not done
IF-Sepharose	—	+	2,048–4,096	1,024	128 (512)	Not done
IF-Sepharose	+	+	4,096	4,096	1,024 (8,192)	32

Mouse L cells were cultivated in 35 mm plastic Petri dishes (5×10^5 cells per dish) in Eagle's minimal essential medium (MEM) and Hanks salt solution, containing 10% calf serum. After removal of medium the cells were washed once with 1 ml PBS and incubated for 1 h at 20° C in the presence of respective lectin solutions in PBS (0.5 ml). Thereafter the lectin solutions were removed and the cells washed once with 1 ml of PBS. IF-Sepharose, prepared as described previously⁴, was treated with lectin by incubating 5×10^4 beads with 0.5 ml lectin solution in PBS for 16 h at 20° C. Thereafter the beads were washed once with 4 ml PBS and suspended in 1 ml MEM without serum. Control Sepharose 4-B beads (Pharmacia Fine Chemicals) were treated identically. IF-Sepharose or control Sepharose beads were then added to the cells (one bead per ten cells) and incubated for 5 h at 37° C. After removal of the beads the cells were challenged with EMC at a multiplicity of infection of 0.1. (In the experiment with con A the cells were washed once with 1 ml of 0.5 M α -methyl mannoside PBS before infection with virus to minimise toxic effects of con A.) Viral yield was determined after 16 h of incubation at 37° C by haemagglutination of human red blood cells of type O in serial two-fold dilutions of virus suspensions⁵. The numbers represent the reciprocal of the highest dilution that showed haemagglutination. The lectin preparations were used at the following protein concentrations⁷: PHA (Phytohaemagglutinin, M form, Grand Island Biological Co.), 4.1 mg⁻¹ ml; con A (A grade, Calbiochem), 1.6 mg⁻¹ ml; lotus lectin (Fucose-Binding Protein, Miles), 0.22 mg⁻¹ ml or 0.67 mg⁻¹ ml (in parentheses). Orange lectin (prepared from Osage orange seeds according to Ahmed *et al.*⁸, using the material precipitating between 0–85% ammonium sulphate saturation after dialysis against PBS), 12 mg⁻¹ ml. The same negative results as shown for Orange lectin were obtained with partially purified lectins from *Lens culinaris* and *Ulex europaeus*. Lens lectin was prepared as described by Sage and Green⁹; crude extracts were fractionated with ammonium sulphate and the fraction precipitating between 33 and 66% saturation was dialysed against water. The resulting precipitate was dissolved in PBS to a protein concentration of 22 mg⁻¹ ml. Extracts of *Ulex europaeus* seeds were fractionated with ammonium sulphate as described by Osawa and Matsumoto¹⁰. Crude haemagglutinin 1 and 2 separating at 0–40 and 40–70% ammonium sulphate saturation were dialysed against PBS and used at protein concentrations of 4.5 and 7.5 mg⁻¹ ml, respectively. When assayed in serial twofold dilutions, all lectin solutions used agglutinated human red blood cells, type O, at maximal dilutions of 1/64–1/128, except the orange lectin solution, which gave haemagglutination at a maximal dilution at 1/512.

bound to Sepharose beads, retained full antiviral activity, even after multiple cell-to-cell transfers⁴. Physical restriction of Sepharose-bound interferon to a well defined area on the cell monolayer protected only cells in immediate contact with the insoluble interferon preparation, but not those unable to make such contacts. This excluded the possibility that soluble interferon diffused from the Sepharose beads to which it was attached⁶. If indeed interferon induces its antiviral effect by interaction with the cell surface, interferon-sensitive cells should possess specific receptor sites. We report here the inhibitory action of certain plant lectins on the action of interferon.

We used Sepharose-bound interferon (IF-Sepharose) to assay for possible inhibitory effects of plant lectins on the induction of the antiviral state. This approach facilitates

removal of unabsorbed lectin by simple washing, which is not possible with soluble interferon. Either mouse L cells, IF-Sepharose or both were preincubated with a solution of lectin in phosphate-buffered saline (PBS). In control experiments Sepharose 4-B beads were treated identically. IF-Sepharose or equal quantities of control beads were then incubated with mouse L cells for 5 h at 37° C in serum-free medium. After removal of the beads, the cells were challenged with encephalomyocarditis virus (EMC) and viral yield was determined by haemagglutination (Table 1).

Lectins derived from *Canavalia ensiformis* (concanavalin A, con A), *Phaseolus vulgaris* (phytohaemagglutinin, PHA) and *Lotus tetragonolobus* (lotus lectin) abolished the antiviral effect of IF-Sepharose, when both IF-Sepharose and the cell monolayer were preincubated. No effects were seen with lectins

Table 2 Reversal of interferon inhibitory action of lectins by lectin-specific substances

Lectin bound to IF-Sepharose	cells	Treatment with	Viral yield
—	—	None	32–64
—	PHA	None	2,048–4,096
—	PHA	D-galactose	2,048–4,096
—	PHA	Fetuin	256
Con A	—	None	2,048–4,096
Con A	—	D-galactose	4,096
Con A	—	α -Methyl-mannoside	256
—	Con A	None	2,048
—	Con A	D-galactose	2,048
—	Con A	α -Methyl-mannoside	64

L cell monolayers or IF-Sepharose beads were incubated with lectin solutions as described under Table 1. Cells were washed once with 1 ml PBS, followed by incubation with 0.5 M D-galactose, 0.5 M α -methyl mannoside, or 10 mg⁻¹ ml Fetuin (Sigma) in PBS. After 15 min at 20° C the saccharide or glycoprotein solutions were removed, cells were washed once with 1 ml PBS and incubated with fresh IF-Sepharose beads as described under Table 1. Con A-treated IF-Sepharose beads were washed with 4 ml PBS, then incubated for 15 min at 20° C with 1 ml D-galactose (0.5 M) or α -methyl mannoside (0.5 M), followed by washing with 4 ml PBS. The washed IF-Sepharose beads were then layered on to L cell monolayers and their antiviral activity was determined as described in Table 1.

derived from Osage orange seeds, *Lens culinaris* and *Ulex europaeus* when used under comparable conditions. When only the cell monolayer was preincubated with lectin, PHA still inhibited interferon action completely, whereas con A and lotus lectin were less inhibitory. In contrast, preincubation of IF-Sepharose alone had little effect in the case of PHA, yet pronounced effects were seen with con A and lotus lectin. The haemagglutinating titres of the lectin solutions used, when assayed with human red cells of group O, were quite comparable. They remained unchanged when the lectin solutions were titrated after preincubation with cells or beads. Similarly, no significant decrease in protein concentration was found after preincubation with either cells or beads. Therefore the amounts of lectins that remained bound to either cells or beads seem to have been rather small, undetectable in our assay conditions. Preincubation of cells, beads or both with these lectins had no detectable effect on viral yield when determined by haemagglutination (Table 1).

As Table 2 shows, the interferon inhibitory action of PHA was almost completely reversed by fetuin, a glycoprotein with high affinity for this lectin. No reversal was observed after treatment with galactose. Likewise, treatment of con A-preincubated cells or IF-Sepharose beads with α -methylmannoside almost completely restored the antiviral effect of IF-Sepharose. Identical treatment with galactose had no effect. We were unable to reverse the interferon inhibitory action of lotus lectin using solutions of L-fucose, a sugar of high affinity for this lectin. This might indicate that interferon inhibitory action by this lectin either is unrelated to its carbohydrate-binding property, or is due to very tight binding to oligosaccharide components that cannot be replaced by this monosaccharide.

Recent data indicate that mouse interferon is a glycoprotein with strong affinity for con A (ref. 11). Likewise, rabbit interferon has been shown to contain terminal neuraminic acid residues attached to penultimate galactosyl residues¹². Inhibitory effects of lectins on the antiviral action of interferon therefore could be caused by binding to the interferon molecule or to the cell surface. Table 1 suggests that both phenomena are possible.

There was pronounced inhibition of the antiviral activity when only the cells were preincubated with PHA, whereas little inhibition resulted from preincubation of IF-Sepharose alone. In contrast, inhibition by con A was more pronounced after preincubation of IF-Sepharose than after preincubation of the cells, although in the latter case appreciable inhibition was also observed. Inhibition by lotus lectin seems to be analogous to that by con A. The reversal of the interferon inhibitory action of PHA and con A by lectin-specific glycoprotein or saccharide solutions further supports the interpretation that the phenomena observed are due to the carbohydrate-binding properties of these substances.

It has become more apparent that certain peptide hormones exert their effects by interaction with the cell surface without penetration into the cell, chiefly because of Cuatrecasas' work with Sepharose-bound insulin¹³. In the case of insulin, receptor sites on the cell surface have been shown to be carbohydrate-containing macromolecules. These receptor sites bind to specific plant lectins; binding of lectin to the cell surface before addition of insulin blocks or modifies the hormone's action¹⁴. There is a striking parallel between the action of insulin and interferon: both diffuse from the site of formation through the blood stream to distant sites; both remain active when attached to an insoluble support, and both are inhibited by pretreatment of target cells with plant lectins. Although it is conceivable that the interferon inhibitory action of PHA is due entirely to specific binding of the lectin to interferon receptor sites on the cell surface, interpretations based on non-specific steric effects or electrostatic charge effects produced by the bound lectin are possible. Whether interferon-specific receptor molecules can be isolated from the cell membrane of interferon-sensitive cells and whether these molecules indeed bind to PHA and related lectins, remains to be established.

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Actinomycin D-induced breakage of human KB cell DNA

ACTINOMYCIN D is a potent inhibitor of RNA synthesis both *in vitro* and *in vivo*^{1,2}. Its mode of action involves the intercalation with DNA at G-C regions and prevention of polymerase movement along the template^{3,4}. Actinomycin D has also been shown to inhibit DNA synthesis, cell division and colony formation in mouse L cells⁵. We have studied the effects of this drug on the DNA of human KB cells in culture. Extensive DNA breakage was induced even at quite low concentrations of the drug.

When human KB (carcinoma of the nasopharynx) cells were treated with different concentrations of actinomycin D for 2.5 h, the rate of DNA synthesis, as measured by the incorporation of ³H-thymidine was greatly reduced at a concentration as low as 0.01 $\mu\text{g ml}^{-1}$ (Fig. 1). At concentrations greater than 10 $\mu\text{g ml}^{-1}$, DNA synthesis was inhibited completely.

To determine the effects of the drug on DNA breakage, cells were prelabelled with ³H-thymidine and treated with actinomycin D for 3 h. The cells were then lysed and the DNA was analysed by alkaline sucrose gradient centrifugation⁶. Figure 2 shows that fragmentation of DNA was induced by the drug at a concentration as low as 0.01 $\mu\text{g ml}^{-1}$. Moreover, the size of the fragments decreased with increasing concentrations of the drug. Figure 3 shows that increasing the treatment time with 10 $\mu\text{g ml}^{-1}$ of actinomycin D resulted in more extensive fragmentation of the DNA.

When fragmentation of DNA occurred the treated cells were

completely attached to the surface of tissue culture flasks. Less than 1% of the cells survived, however, at concentrations higher than $0.1 \mu\text{g ml}^{-1}$ of the drug as measured by colony formation (Table 1). It is possible that fragmentation of the DNA contributes to inhibition of DNA synthesis and loss of cell viability.

The possibility of DNA repair after removal of the drug was examined next. Cells prelabelled with ^3H -thymidine were treated with actinomycin D for 3 h, washed extensively with phosphate buffer saline, and incubated at 37°C for 10 h in growth medium in the absence of the drug. The DNA was then analysed by alkaline sucrose gradient centrifugation (Fig. 4). A comparison

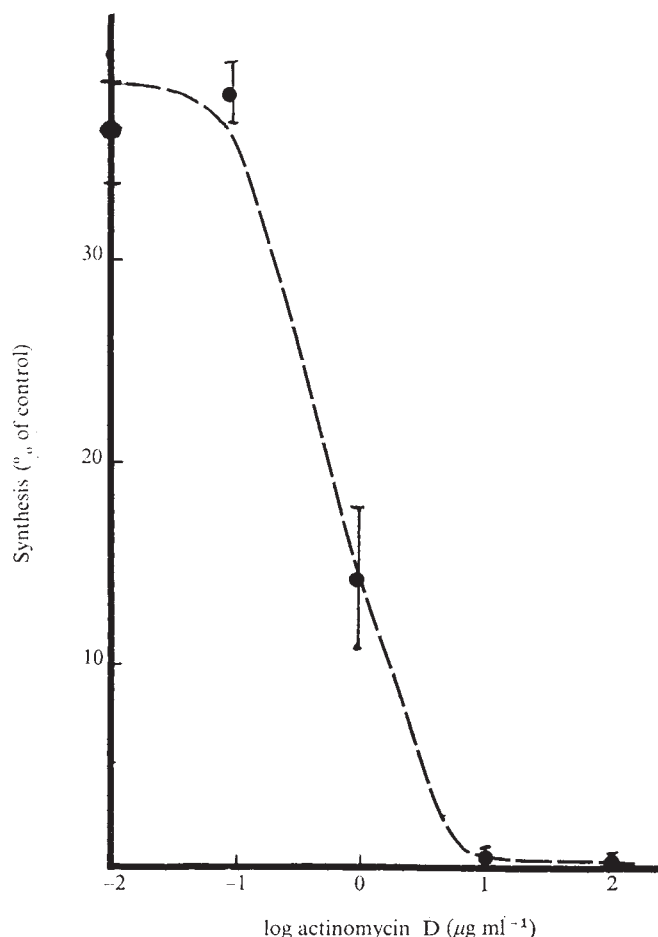


Fig. 1 Human KB cells grown on monolayers were trypsinised and 10^6 of them in 5 ml of alpha minimal essential medium (flow laboratories) + 10% foetal calf serum were seeded in 25 cm^2 Falcon tissue culture flasks and allowed to attach for 1 h at 37°C . Actinomycin D (Merck, Sharpe and Dohme) was then added. After 2 h, ^3H -thymidine (5 Ci mmol^{-1} , Amersham) was added to give a final concentration of $1 \mu\text{Ci ml}^{-1}$ and incubated for a further 30 min. The medium was then removed and the cells were lysed with 1% sodium dodecyl sulphate after washing with phosphate-buffered saline (PBS). The lysate was treated with cold 5% trichloroacetic acid (TCA) and the precipitate collected on to nitrocellulose filters. The radioactivity was determined by liquid scintillation counting. The amount of radioactivity incorporated into the control cells was 1.05×10^5 c.p.m. per 10^6 cells.

of Fig. 4 with Fig. 2 indicated that there was no DNA repair under the conditions of our experiments. Instead, the DNA was fragmented further at concentrations greater than $0.1 \mu\text{g ml}^{-1}$ of actinomycin D. These data suggest that breakage of DNA by the drug at concentrations greater than $0.1 \mu\text{g ml}^{-1}$ is irreversible. This irreversibility could, however, be due to persistence of the drug in these cells since no information on the elution profile of actinomycin D from these cells is available.

The mechanism of cellular DNA breakage by treatment with actinomycin D is not known. It is possible that *in vivo* binding of this drug to DNA induces distortion in the helix⁷ such that attack by nucleases is facilitated. This suggestion is compatible

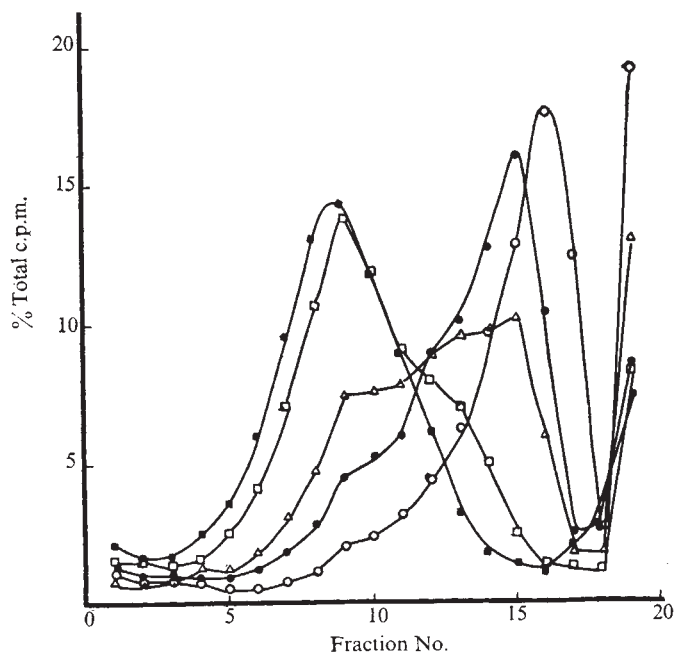


Fig. 2 Human KB cells prelabelled with ^3H -thymidine ($0.5 \mu\text{Ci ml}^{-1}$) for 12 h were treated with actinomycin D for 3 h as described in Fig. 1. The cells were trypsinised, washed and resuspended in PBS. About 2×10^4 – 4×10^4 of them were layered on to a 0.5 ml lysing solution containing 0.5 M NaOH, 0.2% SDS, and 0.01 M ethylenediaminetetraacetic acid (EDTA) on top of a 5–20% alkaline sucrose gradient containing 0.3 M NaOH, 0.01% SDS, 0.001 M EDTA. They were left to lyse for 12 h, and then centrifuged using a SW27.1 rotor in a Beckman ultracentrifuge at 20,000 r.p.m. for 6.5 h at 20°C . One-hundred-drop fractions were collected from the bottom of the tube. Radioactivity in each fraction was determined after cold TCA precipitation. Actinomycin D concentration ($\mu\text{g ml}^{-1}$): $\circ$, 0; $\bullet$, 0.1 (0.1 also similar to 0.01); Δ , 1; $\square$, 10; $\blacksquare$, 100. (Direction of centrifugation from left to right.)

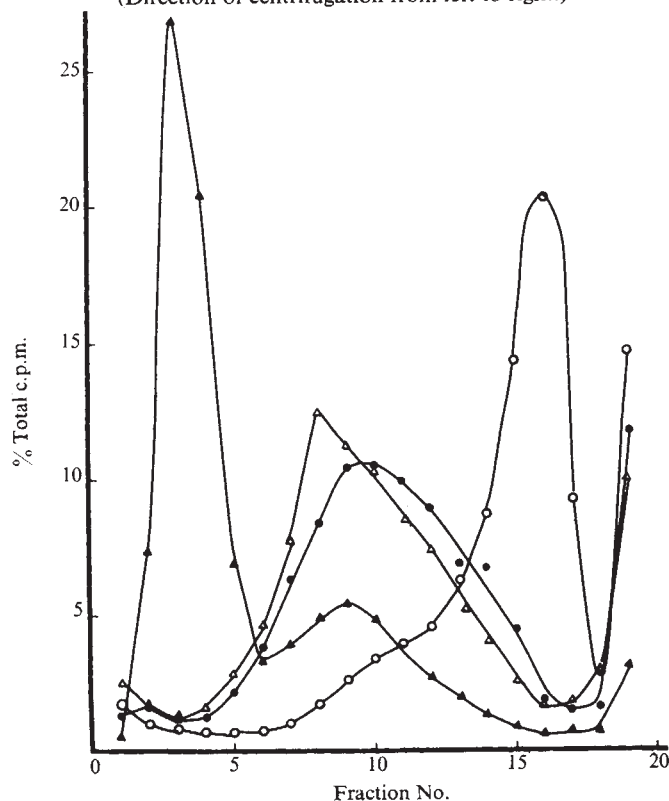


Fig. 3 The cells were prelabelled as described in Fig. 2 and incubated in the presence of actinomycin D at a concentration of $10 \mu\text{g ml}^{-1}$ for the indicated times. The DNA was analysed by alkaline sucrose gradient centrifugation as in Fig. 2. Duration of treatment (h): $\circ$, 0; $\bullet$, 1; Δ , 2.5; $\blacktriangle$, 10.

Table 1 Effect of various concentrations of actinomycin D on cell survival

Actinomycin D ($\mu\text{g ml}^{-1}$)	Average no. of colonies per plate
Control	150
.01	57
.1	0
1	0
10	0
100	0

Triplicate aliquots of 250 cells in 3 ml of α MEM plus 10% FCS were seeded in 60 $\times$ 15 mm Flacon tissue culture dishes and allowed to attach and grow overnight. The medium was replaced by fresh medium containing the given concentration of actinomycin D. After 3 h of incubation, the cells were washed and growth medium was added. The number of colonies per plate was determined after 6 d of growth.

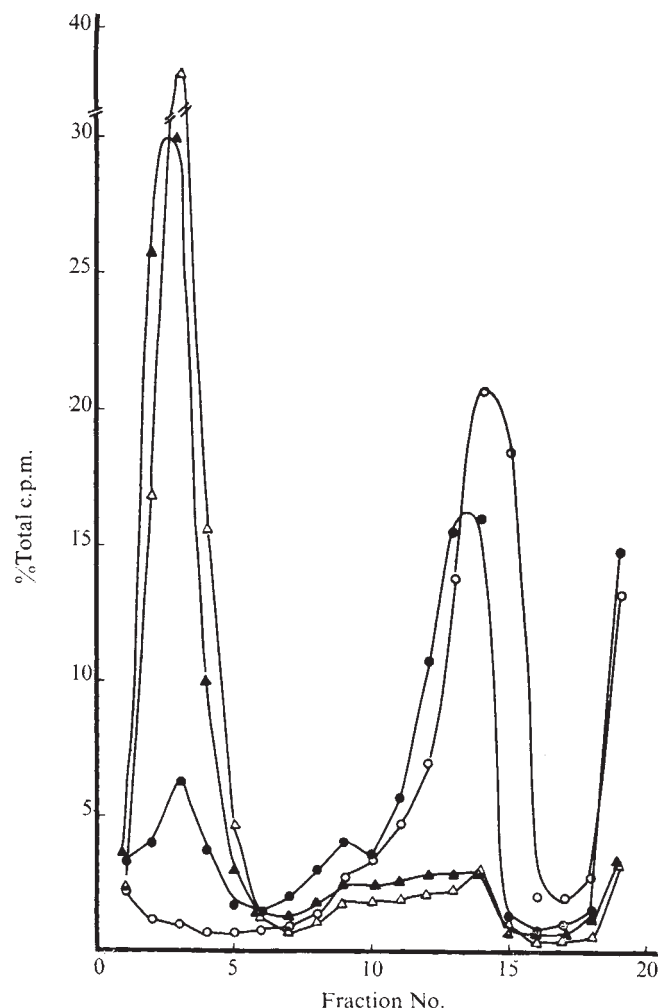


Fig. 4 The cells were prelabelled as described in Fig. 2 and incubated in the presence of actinomycin D for 3 h. The medium was removed and the cells were washed with 2×10 ml medium every 30 min for 2.5 h and incubated for 10 h further. The DNA was then analysed by alkaline sucrose gradient centrifugation. Actinomycin D concentration ($\mu\text{g ml}^{-1}$): $\circ$, 0; $\bullet$, 0.1; Δ , 1; $\blacktriangle$, 10.

with the fact that the DNA breakage induced by actinomycin D has not been observed *in vitro*^{8,9}.

Actinomycin D, at various concentrations, has been used to inhibit RNA synthesis and to examine the effects of this inhibition on other cellular functions. Data presented here and elsewhere¹⁰ suggest that caution is necessary in the interpretation of results obtained in such studies and that the fragmentation of the genome and its effects on cellular functions must be considered concomitantly. Furthermore, it appears that this drug

interferes with DNA as well as RNA metabolism in mammalian cells. Recently, it has been reported that initiation of protein synthesis is also inhibited¹¹. Thus, this drug may have more diverse effects on metabolic processes than is generally assumed.

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Potential of phytomitogens action by neuraminidase and basic polypeptides

TREATMENT of lymphocytes with neuraminidase enhances their blastogenic response to some antigens and mitogens¹, increases their lectin-induced agglutinability^{2,3}, antigenicity and immunogenicity^{4,5}, alters their homing properties⁶ and renders the cells highly susceptible to the cytolytic effects of alloantibody and complement^{7,8}. These changes might result from the exposure of new sites on the cell surface^{2,3,9}, a reduction in the net surface charge of the cells or a combination of the two effects. Polycations agglutinate different cell types¹⁰⁻¹² and markedly reduce their anodic electrophoretic mobility¹⁰. In order to study the effect of cell surface charge on lymphocyte blastogenic response to phytomitogens the effect of polycations on this process was compared with that of neuraminidase.

The stimulation of ³H-uridine incorporation into RNA in rat lymph node lymphocytes, induced by con A (Fig. 1) and by phytohaemagglutinin (PHA) (Fig. 2), was enhanced after treatment of the cells with neuraminidase. In the experimental conditions, outlined in the legend to Fig. 1, 2.2 μg of sialic acid is released per 10^8 cells. This is equal to the total amount of sialic acid which can be released by neuraminidase action. The enhancing effect of neuraminidase was more apparent upon treatment of the cells with low concentrations of the phytomitogens. Like neuraminidase, basic polypeptides were also found to enhance blastogenesis induced by phytomitogens. Poly-L-ornithine and Poly-D-lysine were used in this study as they are resistant to degradation by proteolytic enzymes¹³. As shown in Fig. 3a, poly-L-ornithine enhances the stimulation of ³H-uridine incorporation into RNA in rat lymph node lymphocytes induced by con A. A similar effect was obtained upon addition of poly-D-lysine (Fig. 3b). Poly-L-ornithine also enhanced the stimulation of ³H-uridine incorporation into RNA in rat lymphocytes induced by PHA (Fig. 4). The stimulation of ³H-thymidine incorporation into DNA in rat lymph node lymphocytes, induced by con A and by PHA was also enhanced by poly-L-ornithine. The extent of ³H-thymidine

incorporation (c.p.m. $\pm$ s.e.) into control, con A ($0.5 \mu\text{g ml}^{-1}$) or PHA ($0.5 \mu\text{g ml}^{-1}$)-treated rat lymphocytes, after incubation for 48 h, was 800 ± 79 , $32,590 \pm 3,170$ and $33,710 \pm 6,010$, respectively. ^3H -thymidine incorporation into similar cultures incubated in the presence of poly-L-ornithine ($1 \mu\text{g ml}^{-1}$) was 742 ± 44 , $62,970 \pm 7,190$ and $80,260 \pm 5,680$, respectively. The basic polypeptides alone did not stimulate the cells. In the experimental conditions outlined in Fig. 3a, poly-L-ornithine did not enhance the response of neuraminidase-treated cells to con A. As it seemed possible that the effects caused by neuraminidase and by the basic polypeptides might result from an increase in the binding of the lectins to the lymphocytes, I investigated this possibility. Rat lymph node lymphocytes ($5 \times 10^6 \text{ ml}^{-1}$ Dulbecco's modified Eagle's medium, supplemented

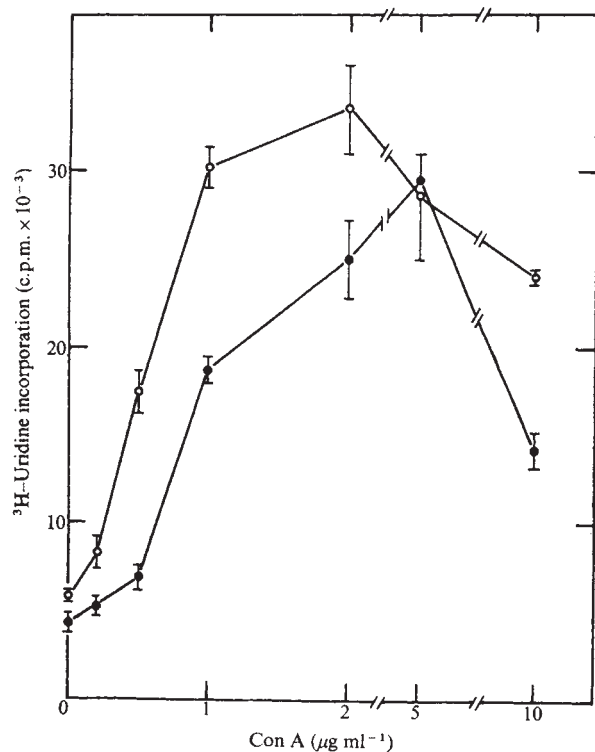


Fig. 1 Effect of neuraminidase on the response of rat lymphocytes to con A. Wistar rat lymph node lymphocytes (10^6 cells ml^{-1} PBS) were incubated with *Vibrio comma* neuraminidase (Behringwerke AG) (50 U ml^{-1}) for 30 min at 37°C . The cells were then washed and suspended ($5 \times 10^6 \text{ ml}^{-1}$) in Dulbecco's modified Eagle's medium, supplemented with horse serum (2%) and incubated as previously described²⁵. ^3H -Uridine incorporation was determined after incubation for 24 h. Con A, twice crystallised (Miles-Yeda) was used. Results are expressed as the mean $\pm$ s.e. of triplicate cultures. O, Neuraminidase-treated cells; ●, control cells.

with horse serum (2%)) were incubated with ^{63}Ni -con A ($1 \mu\text{g ml}^{-1}$) in the absence and presence of poly-L-ornithine ($2 \mu\text{g ml}^{-1}$) at 37°C for 2 h. The specific binding of ^{63}Ni -con A to the cells was determined as previously described¹⁴. In these conditions, 48,000 molecules of con A were bound per cell in the control experiment and neither neuraminidase nor poly-L-ornithine had any effect on the extent of lectin binding.

In contrast to our finding that neuraminidase enhances the response of rat lymph node lymphocytes to PHA, other investigators have found that neuraminidase does not change the response of human lymphocytes to PHA¹ and inhibits PHA-absorptive capacity and PHA response of mouse spleen cells¹⁵. The discrepancies between the data obtained by different groups may be due to species differ-

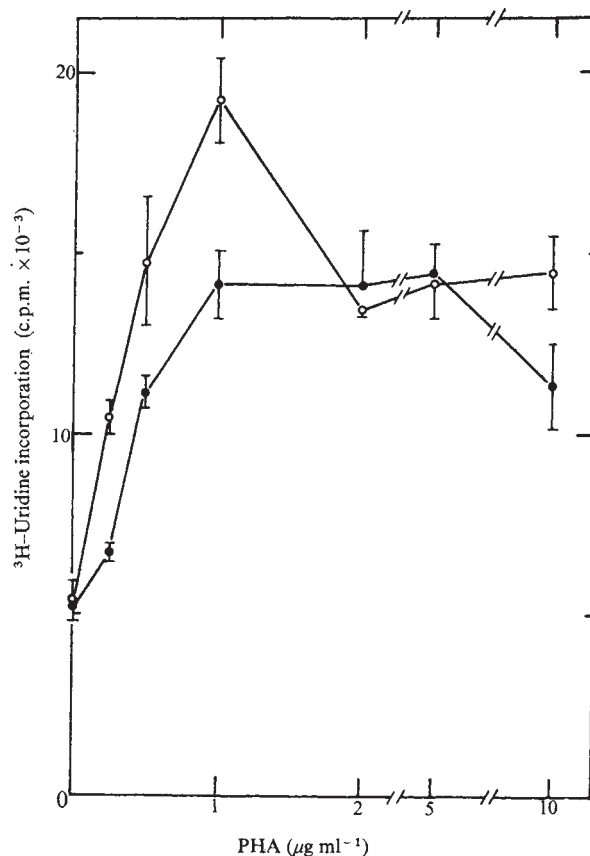


Fig. 2 Effect of neuraminidase on the response of rat lymphocytes to PHA. For experimental details see legend to Fig. 1. Purified PHA from Wellcome was used. O, Neuraminidase-treated cells; ●, control cells.

ences and to the different doses of neuraminidase and PHA used in the various studies. It has been suggested that cross linkage and aggregation of specific membrane sites may be involved in the triggering of lymphocytes to undergo blastogenesis¹⁶⁻¹⁸. Aggregation of membrane sites (most probably glycoproteins) induced by lectins, occurs when the balance of forces favouring aggregation overcomes those which oppose it, like charge repulsion forces. The overall net sur-

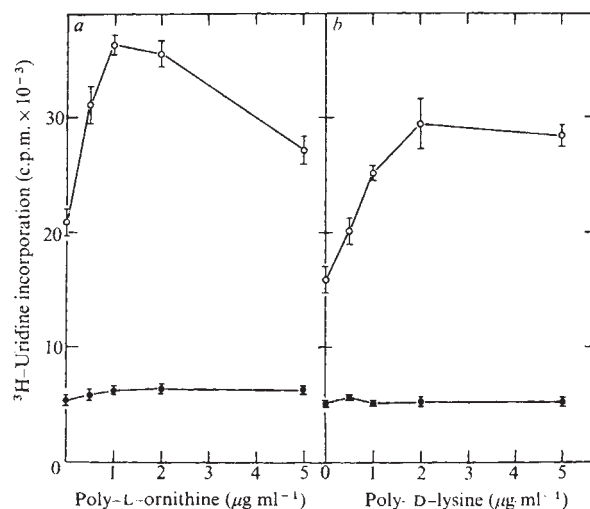


Fig. 3 Effect of basic polypeptides on the response of rat lymphocytes to con A. Cells were cultured in the presence of, a, poly-L-ornithine (average degree of polymerisation (DP = 340) or, b, poly-D-lysine (DP = 380)). O, In the presence of con A ($1 \mu\text{g ml}^{-1}$); ●, control.

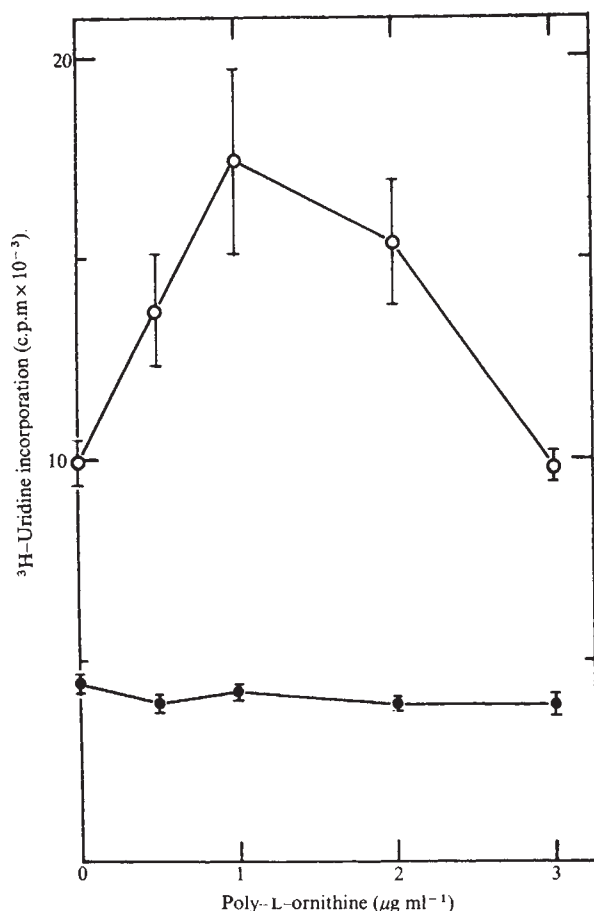


Fig. 4 Effect of poly-L-ornithine on the response of rat lymphocytes to PHA. O, In the presence of PHA (0.5 $\mu\text{g ml}^{-1}$); ●, control.

face charge of the lymphocyte is negative¹⁹ but little is known about the net charge of individual glycoproteins of the lymphocyte membrane. Glycophorin is a glycoprotein isolated from red cell ghost which carries the receptors for the plant lectins PHA and wheat germ agglutinin and contains 60% carbohydrate and 25% sialic acid by weight^{20,21}. If the lymphocyte receptors for con A and PHA were of a similar chemical nature, it might be expected that both neuraminidase treatment and polycations would facilitate their lectin-induced aggregation, by reducing charge repulsion. The enhancing effect of neuraminidase and basic polyamino acids on phytomitogens-induced transformation might also result from an increase in cell aggregation induced by either of these agents. Cell contact has been

shown to increase mitogen-stimulation of lymphocytes²². Neuraminidase treatment has a marked effect also on some cellular properties of non-lymphoid cells^{23,24}. It might be of interest to compare the effect of neuraminidase with that of polycations in a variety of biological systems. This approach might help to elucidate whether an observed effect induced by neuraminidase results primarily from a reduction in the surface charge or results from exposure of new sites on the cell membrane.

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Erratum

In the article "Dynamic evidence on massive coronas of

galaxies" by J. Einasto, A. Kaasik and E. Saar (*Nature*, **250**, 309; 1974) Tables 1 and 2 were inadvertently omitted.

Table 1 Parameters of galactic populations (individual galaxies)

Galaxy	L_s ($10^{10} L_\odot$)	M_s ($10^{10} M_\odot$)	M_c ($10^{10} M_\odot$)	R_{vir} (kpc)	$-\log p_c$ (g cm ⁻³)
NGC224	2.0	17	> 35	> 14	24.58
NGC300	0.45	2.0	> 2.9	> 6	24.60
NGC598	0.32	1.5	> 2.8	> 6	24.54
NGC3031	1.8	12	> 21	> 11	24.52
IC342	4.9	12	> 34	> 13	24.55

Table 2 Parameters of galactic populations (pairs of galaxies)

Type of primary galaxy	$\langle L_s \rangle$ ($10^{10} L_\odot$)	$\langle M_s \rangle$ ($10^{10} M_\odot$)	$\langle M_c \rangle$ ($10^{10} M_\odot$)	$\langle R_{vir} \rangle$ (kpc)	No. of pairs
Spiral (intermediate)	3.8	38	350	25	33
Spiral (bright)	15	150	1,600	47	32
Elliptical	12	250	$\geq 1,500$	≥ 46	40

matters arising

Blocking one-way maternal-foetal MLR

SIR,—The results of animal experiments^{1,2} show that enhancing or blocking antibodies may be at least partly responsible for the apparent lack of maternal immunological response to the paternally derived histocompatibility factors of the foetus. Youtananukorn and Matangkasombut³ used peripheral blood from normal *post partum* women to demonstrate that migration inhibition of maternal leukocytes occurred in the presence of pooled placental antigens. This response was completely blocked in the presence of autologous plasma but was unaffected by plasma from unrelated *post partum* women. We have used the one-way mixed lymphocyte reaction (MLR) between maternal (responding) and mitomycin-treated (stimulating) foetal cells obtained from cord blood to investigate the possible blocking effect of autologous maternal plasma.

Peripheral venous blood samples were collected at the end of labour from 12 women who had normal pregnancies and labours. Samples of cord blood were obtained at the same time, taking care to avoid contamination with maternal blood. Lymphocytes were separated from the heparinised blood samples by erythrocyte sedimentation in Plasmagel (Roger Bellon Laboratories). Cord blood lymphocytes were incubated at a concentration of $10 \times 10^6 \text{ ml}^{-1}$ in mitomycin C ($25 \mu\text{g ml}^{-1}$) for 20 min at 37°C and then washed three times in Eagle's MEM medium⁴. MLR

was then performed using the method previously described⁵. Results are summarised in the Table (figures in parentheses are standard deviations).

Autologous maternal plasma produced a significant inhibition of maternal lymphocyte transformation to stimulation by foetal lymphocytes in 3 out of 12 cases, while no significant effect was produced in control cultures containing homologous maternal plasma. In the presence of pooled male serum, a mixed lymphocyte reactivity of more than two occurred in only four out of twelve cases. This suggests the possibility that previous exposure of maternal lymphocytes to blocking factors *in vivo* might be partly responsible for their low responsiveness to foetal lymphocytes *in vitro*.

This might explain why autologous maternal plasma only produced a significant inhibition of response in those cases with a high mixed lymphocyte reactivity. It would also account for the apparent discrepancy between our findings and those of Youtananukorn and Matangkasombut³, since there might be different mechanisms whereby blocking factors produce their effects on lymphocyte transformation and leukocyte migration inhibition.

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A reply will be published in a forthcoming issue.

On the origins of molecular biology

SIR,—We wish to respond to the *Nature* supplement of April 26 entitled, "Molecular Biology Comes of Age". This gives the misleading impression that a specific date¹ can be placed on the birth of molecular biology. We suggest there are earlier origins for a true molecular biology.

In 1867 Spencer wrote in *Principles of Biology*:

"We have seen it to be a necessary inference from various orders of facts, that organisms are built up of certain highly-complex molecules which we distinguish as physiological units—each kind of organism being built up of physiological units peculiar to itself²."

Forerunners of present concepts of molecular biology were proposed in the period 1860–1910 by Karl Nageli

Table 1 Results of the one-way MLR

One way MLR in pooled male serum	Mean 10 min count in pooled male serum	Mean 10 min count in autologous maternal plasma	Effect of autologous maternal plasma (%)	Probability	Mean 10 min count in homologous maternal plasma	Effect of homologous maternal plasma (%)	Probability
2.2	1,200 (249)	459 (74)	38	0.01–0.02	773 (198)	64	NS
0.8	387 (70)	550 (173)	142	NS	526 (24)	136	NS
0.7	520 (72)	627 (72)	121	NS	909 (495)	175	NS
9.8	3,089 (719)	3,193 (1,058)	103	NS	2,530 (91)	81	NS
1.1	361 (89)	421 (36)	117	NS	379 (108)	104	NS
2.0	502 (125)	548 (170)	109	NS	252 (72)	50	NS
1.0	478 (57)	491 (72)	103	NS	398 (51)	83	NS
1.1	338 (75)	316 (29)	94	NS	421 (109)	124	NS
0.8	283 (54)	294 (37)	104	NS	272 (79)	96	NS
1.4	703 (121)	344 (63)	49	0.02–0.05	619 (272)	88	NS
0.8	524 (147)	346 (46)	66	NS	536 (148)	102	NS
3.8	2,007 (601)	572 (227)	29	0.02–0.05	1,242 (1,194)	62	NS

3.25×10^6 maternal (responding) and 3.25×10^6 foetal (stimulating) cells were cultured in 3 ml of Eagle's MEM medium (pH 7.2) enriched with 1 ml of 2 mM L-glutamine per 100 ml, for 7 d. Test cultures (in triplicate) contained 15% complement-inactivated autologous maternal plasma. Two sets of control cultures (each in triplicate) contained 15% complement-inactivated homologous maternal plasma, and 15% pooled male serum respectively. Maternal and cord blood lymphocytes were cultured separately in triplicate, to assess spontaneous transformation. Mixed lymphocyte reactivity is expressed as the ratio of the mean of the triplicate counts of the mixed cultures to the mean of the triplicate counts of the separate maternal and foetal cell cultures. The effects of autologous and homologous maternal plasma are expressed as percentages of the ratio of the mean triplicate counts of the mixed cell cultures in autologous and homologous plasma respectively, to the mean of the triplicate counts of the mixed cell cultures in pooled male serum. NS, Not significant.

(quoted in ref. 3), August Weismann⁴, Edmund Wilson⁵ and Hugo de Vries⁶, among others.

The early origins of molecular biology discussed by Gunther Stent⁷ and others emphasise the desire to apply laws much like those of physics to biology. In this regard, Erwin Schrödinger's book *What is Life?*⁸ was influential. Fifteen years before the publication of Schrödinger's book, the well-known biologist Edmund Wilson wrote a book with a similar intention entitled *The Physical Basis of Life*⁹.

Whereas a preoccupation with physics may have motivated the so-called "phage group"¹⁰ there was a separate origin for the application of physicochemical methods to studies of the structures of biological molecules¹¹. W. Astbury, an X-ray crystallographer, clearly played a major part in this, and indeed was the first to coin the term molecular biology¹². In addition, it is not generally realised that in 1949 Sven Furberg, a Norwegian graduate student in the laboratory of J. D. Bernal, was the first to propose a helical structure for DNA, albeit single-stranded, on the basis of X-ray studies on nucleosides¹³.

We thus conclude that it is somewhat difficult to set a precise date for the origin of molecular biology, but we presume that by April 25, 1953, molecular biology had already come of age.

Yours faithfully,

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DNA synthesis in plants

SIR,—Buchowicz¹ reports "that incorporation of thymidine into DNA of germinating wheat seeds begins only after some preliminary activation of RNA synthesis is completed, implying an RNA-dependent DNA synthesis".

I do not agree with this conclusion. Indeed, it has only been demonstrated that RNA synthesis precedes DNA synthesis^{2,3} and that inhibition of protein synthesis between 0 and 9 h results in a complete suppression of DNA synthesis. These essential proteins are probably coded for by pre-formed mRNA^{4,5}. Thus, it is not at all evident that DNA synthesis is dependent on RNA in this way. Thymidine is not incorporated into DNA before a lag period in germinating wheat because, as in other plants, the phosphorylating enzymes are lacking in dry seeds^{6,7}. They become detectable a few hours before the onset of DNA synthesis^{7,8}. In contrast, uridine can be phosphorylated by extracts of dry seeds^{8,9}.

I wish to draw your attention to my interpretation of Dr Buchowicz's results. A prerequisite to check whether the cytoplasm may be an early site of nuclear DNA synthesis is to obtain a cytoplasmic fraction free of nuclear contamination. I have frequently obtained significant ¹⁴C-thymidine labellings in similar 'cytoplasmic fractions' with radish seedlings, but all the electron microscope controls I have performed have revealed that nuclei were broken in the 1,000g pellet, and that successive 15,000g and 27,000g pellets still contained chromatin. The difficulty of isolating unbroken plant nuclei is well known amongst plant biochemists, and this is the reason why I believe that most of the radioactivity detected by Dr Buchowicz in his cytoplasmic fraction is of nuclear origin.

The higher specific activity of the cytoplasmic fraction can be explained if we assume that newly synthesised, short, DNA fragments are probably more easily released from broken nuclei than highly polymerised DNA from chromatin. One way to check whether the cytoplasmic fraction is free of nuclear contamination would

be to assay this fraction for nuclear enzymatic activities such as RNA polymerase.

Yours faithfully,

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¹ Buchowicz, J., *Nature*, **249**, 350 (1974).

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DR BUCHOWICZ REPLIES: I was interested to learn that Dr Delseny had observed similar labelling of cytoplasmic DNA in radish seedlings.

The possibility of nuclear contamination of the 'cytoplasmic fraction' has not been overlooked in my letter¹. Instead, it was found insignificant, as the cytoplasmic radioactivity dropped when the possible source of contamination, radioactivity of nuclear DNA, increased. The comments concerning the dependence of DNA synthesis on thymidine kinase activity are obviously important. Nevertheless, the DNA synthesis would proceed without the participation of thymidine kinase (deriving TMP from UMP reduction and methylation) if not limited by other factors. It is known, however, that other precursors as well as thymidine are not incorporated into DNA at early germination stages, in spite of the fact that enzymes catalysing UMP synthesis² and reduction³ are active. It seemed, therefore, justified to point out that the initiation of DNA synthesis in awakening wheat embryo may depend on the appearance of a newly synthesised RNA fraction.

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reviews

Scientific laws and logic

The Structure of Scientific Inference. By Mary Hesse. Pp. vii+309. (Macmillan: London and Basingstoke, April 1974.) £5.95.

IN this book Dr Hesse develops a logic of science. She is concerned for the most part with inference. One might expect however, that some account of scientific theories would be adopted as a starting point because theories are involved in most scientific inference. The account of theories will to some extent determine the characteristic patterns of inference. For example, if it is held that theories are partially interpreted deductive systems, then inference from theory to observable consequence will be deductive. In common with an increasing number of contemporary writers Dr Hesse rejects this formalist view. As an alternative a network model of theories is proposed (page 4):

"Briefly, the model interprets a scientific theory in terms of a network of concepts related by laws, in which only pragmatic and relative distinctions can be made between 'theoretical' and 'observational'. Some lawlike statements of the theory can be tested relatively directly by observation, but which these are may depend on the current state of the whole theory and whether an observation statement is accepted as 'true' or 'false' in any given case may also depend on the coherence of the observation statement with the rest of the currently accepted theory."

This implies that the acceptance or rejection of a given observation statement may depend on current theoretical considerations. These may change, and so we may come to reject as false a statement previously accepted as true. Dr Hesse mentions that the network model owes much to Quine and Duhem. This is clearly true.

The Quine-Duhem thesis and related views are by no means unproblematical. Suppose we want to reject as false the observation statement "The individual x_1 is red" which we had previously accepted. If x_1 and all those other individuals $x_2, x_3, \dots$ which were previously said to be red still retain the same colour as before, then if x_1 is no longer red then neither are $x_2, x_3, \dots$, on the assumption that all the individuals have the same colour, hence nothing is red. If necessary some new word could be invented to describe this colour. Dr Hesse is not committed to this trivial view because on her account of how we learn to use words such as

red we recognise that individuals are similar to each other to an unspecified degree. Thus theoretical considerations may suggest that after all x_1 is not sufficiently similar to $x_2, x_3, \dots$ to be called red. But if 'similar' is always taken to be 'similar in a given respect', as it is by Popper, then this implies that there are no degrees of similarity and also that 'similar' is transitive. There are of course, differences within the class of red objects in that there are shades of red, but degrees of redness in this sense does not imply degrees of similarity among red objects. Dr Hesse discusses similarity at some length; in particular she defends her account against a Popperian view. It is unfortunately not possible to do justice to her arguments in a short review.

Dr Hesse's account of theories leads her to discuss inductive and analogical inference; this involves a discussion of arguments from particular to general and from particular to particular. In the context of a logic of science these concern the confirmation of theories and predictions by evidence. Dr Hesse does not attempt to justify non-deductive inference, but rather she gives an explication of the intuitive inductive rules used by scientists. An explication is the process of formulating precise rules of use, possibly expressed in a formalised system, for an imprecise concept which is used in some domain of discourse. The explication may suggest revisions in the use of the concept in question or in the use of related concepts. Dr Hesse sees the problem of induction as falling into two parts: (1) to formulate a set of inductive rules; (2) to formalise these. She concentrates on (2). In the light of the network model she suggests that the axioms of probability are best adapted to explicate inductive practices. Probability is interpreted in the personalist sense as degree of rational belief. Thus the answer to this problem of induction is an acceptable probabilistic confirmation theory.

At least two problems confront a proponent of a probabilistic confirmation theory. First, it is necessary to show that some adequate resolution of the paradoxes of confirmation is possible within the theory. Dr Hesse takes the so-called transitivity paradox to be one of the most general and powerful paradoxes. It suggests that confirmation is not always transitive. We are not, therefore always able to assume that the degree of confirmation of a

theory by certain evidence is passed on to the predictions of the theory. In order to account for our confidence in predictions Dr Hesse interprets theoretical inference as inference from evidence to prediction bypassing theory. The inference is taken to be analogical and the role of the theory is to make explicit the analogy between evidence and prediction. This is a most interesting suggestion.

Second, if a probabilistic confirmation theory is to account for the confirmation of laws, it may be thought necessary to justify the restriction of the scope of laws to finite domains. This restriction, which is a consequence of the explication, is necessary because, given that the language is infinite and that there are no *a priori* reasons for assigning finite initial probability to any finite subset of possible universal generalisations, then no finite amount of evidence will raise the probability of such a generalisation above the initial value of zero required by the probability axioms. Popper and Lakatos have taken this to be a fundamental objection to Carnap's confirmation theory. But Dr Hesse argues that laws are expressed by generalisations of finite scope because it is unreasonable to believe that unrestricted generalisations have any chance of being true and hence that zero probability is appropriate for such generalisations. If restricted generalisations may be assigned non-zero probability, then we would expect that the reason why unrestricted generalisations have zero probability concerns the fact that their scope is unrestricted. But according to Dr Hesse (page 181):

"This is not so much because such a belief covers an infinite number of instances, but rather because it may not be reasonable to believe that U [a Universal generalisation] states a law accurately even in one instance."

If this is true, then it seems to follow that it is unreasonable to believe that a finite generalisation expresses a law accurately. It is not however, obvious that it is reasonable for scientists to be convinced (probability=1) that all universal generalisations are false. If it is held that some laws are expressed by universal generalisations, then we may be inclined to reject an explication which has as a consequence that these laws have zero probability.

Although I think that it is possible to give further arguments in favour of these criticisms of Dr Hesse's logic of science, this is not to say that Dr

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Hesse's book is not an interesting and original contribution to the philosophy of science. It is therefore to be recommended to the advanced student, though to one who is not familiar with the subject it may prove a little difficult.

JOHN FORGE

Television tomorrow

Television: Technology and Cultural Form. By Raymond Williams. Pp. 160. (Fontana/Collins: London, 1974.) 45p.

WHEN Raymond Williams was television critic of *The Listener*, he tried to appraise television as a phenomenon in spite of the convention among reviewers that what counts are programmes, as isolated units. In this book he is able to stand back and take a very long view. Television—what is it? Technology, or social force? What does the experience of watching television consist of? How did the institutions of broadcasting develop out of the technology and what kinds of institutions may arise to serve up television in its new forms—video cassettes, cable television, international broadcasting?

The author (now reader in drama at Oxford) concludes that there was nothing inevitable in television's emergence as a form of mass entertainment consumed by individuals in the privacy of their homes. He does not swallow the argument that "I Love Lucy" was as inherent in the vacuum tube as some believe the atomic bomb was in the splitting of the atom. Television, he maintains, emerged in its present form because it was under the control of the broadcasting institutions that had developed radio. And radio's growth was determined, even forced, by the equipment manufacturing industry. But between the two media (it is possible to use the word in the plural) there is a profound difference. Radio is cheap. Television is expensive. And the contradiction remains. No country, even the United Kingdom, has satisfactorily solved it. How to recover the enormous costs of television from a mass audience of individual viewers?

Mr. Williams devotes a long chapter to the comparative incidence of various types of television programmes on five television channels—three British and two American—during a single week. The results are hardly surprising. (BBC1 led the pack in public affairs discussions, with 8.3 hours, while Channel 7 in San Francisco was tops in commercials, with 18.4 hours.) A mild point made by the author is that the formal category of programme matters less than its manner. A serious documentary may be trivialised. A panel quiz game may illuminate rela-

tionships between husband and wife.

The most interesting thesis of Mr Williams's book, to my mind, is the idea that television is the whole package. He calls it "flow". The programmes, news and weather breaks, commercials, trailers for later programmes, the lot. By this standard, the BBC is full of commercials—for itself. He is amusing when he recounts the difficulty, in Miami, in trying to follow the plot of an old movie. Not only were the advertisements inserted more frequently as the viewer became hooked on the programme but there were added as well trailers of two other old films, to be shown on subsequent nights. He also observes that on the San Francisco channel, the news that some pharmaceutical companies had been accused of false advertising claims was part of the same news bulletin that contained a commercial for a pain killer.

Looking ahead, Mr Williams is worried by the paradox presented by the new technology. He sees the promise of cable (multi-channelled, wired) television and international satellite broadcasting as that of democratising communications, of bringing a new universal accessibility to television. Yet he sees (by looking back) that these developments could be stifled by existing broadcasting organisations, by international advertisers and governments. At the same time he sees that uncontrolled development of cable television could destroy what is good in national broadcasting. His main suggestion is that there should be more independent television production companies. These could diminish, without destroying, national broadcasting while providing content for cable systems to transmit. Cable he would have as a national utility.

There are a few quibbles one must make. Cable television will not be universally available in the United States by 1980. And it is unlikely to reach 30% of television homes in Britain by that time either. Its growth has been stopped dead, by restrictive rules and by shortage of investment capital. Similarly, the author's recommendation that proper international agreements on satellite television should not involve bodies with weighted voting (like Intelsat) is unrealistic. The fact is that, as the United Nations' experience has shown, a system of one vote to a country is a form of weighted voting itself, for it allows small countries a disproportionate influence from sheer numbers.

It is a pity that this book is not more readable for there is much in it that will interest media buffs. On the future of British Broadcasting, Lord Annan's committee should find it stimulating.

BRENDA MADDOX

Doctor meets patient

Therapeutics: From the Primitives to the 20th Century, with an Appendix—History of Dietetics. By Erwin H. Ackerknecht. Pp. x+194. (Hafner, Macmillan: New York; Collier Macmillan: London, January 1974.) £6.25.

MEDICAL historians have all too often shown greater interest in what doctors have written than in how they have treated their patients. They have studied medical ideas and theories rather than the ways these ideas have been applied. Certainly, theory fascinates more than praxis. Yet for the patient at least, praxis is the key medical activity, patients being far more concerned with what their physicians can do than with what they know.

Therapeutics is the point where doctor and patient meet. Nevertheless, such has been the neglect of this subject by medical historians that the last general history of therapeutics was published in 1877—a fact which makes Professor Ackerknecht's lucid and stimulating volume all the more welcome. First published in German in 1970, it has now been translated by the author, formerly Director of the Institute of Medical History at the University of Zürich. The book charts the therapeutic programmes and rationales of medicine from the Egyptians to the twentieth century. Ackerknecht's method involves analysis of the therapeutic writings of major medical figures in each particular age: the Hippocratics, Galen, Paracelsus, Sydenham, Laennec, Ehrlich, and so on. In addition, he refers frequently to the works of less well known doctors whose activities and thoughts were equally significant in defining the medical texture of each of his historical portraits. The result is a monograph which is crammed with facts and brimming with ideas.

It is difficult to summarise a book which is so wide ranging. Nevertheless, two recurrent themes should be mentioned. First, as Ackerknecht repeatedly demonstrates, medical theories have been far more flexible than medical therapeutics. Bloodletting, for instance, has been employed in many different settings. The primitives used it. The Greeks recommended it, as did the Indians. Bloodletting was practised in the Middle Ages, the Renaissance and the Enlightenment. In fact only in the middle of the nineteenth century did physicians begin to look critically at this traditional form of therapy. The therapy itself remained essentially unchanged, yet the rationale for this therapeutic procedure could be different for each particular age or culture setting. The same may be said for many other traditional therapies, such as purgatives, cathartics and emetics.

The second historical insight which Ackerknecht brings to bear on his subject concerns the nature of medical experience. In therapeutics, each doctor should be able to form independent evaluations of the effectiveness of his armamentarium. Unfortunately, experience often being no more than 'pseudo-experience', doctors have found that any particular therapeutic regimen yields precisely the results they expected it to. Patients rarely disappoint their physicians if they can help it.

Professor Ackerknecht explores the historical ramifications of these and many other themes in this splendid little book. A full appreciation of it requires some prior acquaintance with the general features of the history of medicine. This can be pleasantly acquired through Ackerknecht's *Short History of Medicine*, published in 1955 but still the best short introduction to the subject available. The remarkable range of his interests may be seen from some of his other contributions to the history of medicine: a biography of Rudolf Virchow, a study of French medicine in the first half of the nineteenth century, a monograph on malaria in the Upper Mississippi Valley, a short history of psychiatry, and a series of classic papers on primitive medicine. These works mark Erwin Ackerknecht as a true cosmopolitan and one of the outstanding medical historians of our time.

W. F. BYNUM

Rejecting behaviourism

The Psychology of Consciousness. By Robert E. Ornstein. Pp. xxi+247. (Freeman: San Francisco, 1972.) \$3.50.

THIS book represents a current swing away from behaviourist psychologies, in which consciousness is ignored or even denied. It criticises Western science, as being over-limited to sequential processes of reasoning at the cost of immediate intuitive understanding, associated with the Eastern approach to studying mind represented by the Chinese I Ching and the meditative and rhythmic exercises of yoga. Dr Ornstein tries to relate East and West, with the neurological notion that (in right handed people) the right cerebral hemisphere serves the artist and dreamer, while the left hemisphere serves sequential logical thinking and language. For this he refers to the important 'split brain' experiments of Roger Sperry, in which the fibres of the corpus callosum, normally joining the hemispheres, are sectioned in serious cases of epilepsy.

Ornstein suggests that the right-hemisphere Eastern culture and the left-hemisphere Western culture can be combined—to make better use of the brain as a whole. Is this a neurological alliance of C. P. Snow's Two Cultures?



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Grassland Ecology and Wildlife Management

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Ornstein refers also to recent experiments on 'biofeedback', in which he has himself made interesting contributions on the control of automatic functions not normally under conscious control. There are also references to anthropological data on different ways that people categorise, describe and see things as evidence for the relativity and perhaps arbitrariness of what is accepted as knowledge.

The book starts by referring to Kuhn's scientific paradigms, as both giving stability to science and belief (analogous to the perceptual constancies) and also as limiting what we can see and understand. To Ornstein, behaviourism's rejection of consciousness, and logical positivism's rejection of statements not susceptible of strict 'scientific' verification as not meaningful, are examples of paradigms so narrow that important understanding is blinkered and lost. Although one may sympathise with Ornstein's dissatisfaction with behaviourism as a paradigm for psychology (however useful it may have been to concentrate experiments on technically feasible enquiry) he does not lay siege with much fact or rigour, except indeed to point to consciousness as a fact that it is absurd to ignore. He seems in places to follow Aldous Huxley in regarding the nervous system as doing not much more than filtering experience—quoting with approval Huxley's remark: "Mind at large has to be funnelled through the reducing valve of the brain and nervous system. What comes out at the other end is a measly trifle of the kind of consciousness which will help us to stay alive on the surface of this particular planet". This is, however, a view far opposed to current theories of perception, as active construction from limited data signalled by the senses—but which Ornstein also espouses. There seems to be a lack of consistency in the book on these questions; but its aim is evidently to loosen what Ornstein regards as constraining bonds of current theories of brain function, rather than attempt at this time to produce a conceptual synthesis, or a consistent working paradigm for psychology. It does have the merit of asking some awkward questions, with suggestions that answers might be found in strange places.

Here we come to the nub of the problem: to the Western reader without experience of 'meditation', the descriptions of conscious states and so on are difficult to comprehend or even to take seriously; but is this because of restricting limits of our experience, and paradigms of what should constitute science? Ornstein puts the matter cogently (page 6): "Science as a mode of knowing involves a limitation on enquiry. The essence of good experiment is successful exclusion". And

later (page 100), reversing the case from a non-technological to a Western society: "Our peasant . . . cannot see why, if it is indeed possible (as we claim) to fly to the planets, he cannot do it now in his own terms . . . When he fails, he will likely come to believe that 'space flight' is really an impossibility, that any one who claims it to be possible is simply gullible, 'unscientific', or even a liar . . . It is similar tendencies in ourselves which we, as Western students of psychology, may need to overcome in investigating an area which is so new, so spectacular, and so unknown to us . . . We should not ignore 'Eastern science' because of its imbalances, or because of the misinterpretations heaped around it". This book presents a case with honesty and with learning which is nevertheless in parts very difficult to comprehend, let alone judge. But if the case were valid, surely this is just what we might expect!

RICHARD L. GREGORY

Highly strung

Development and Regeneration in the Nervous System. Edited by R. M. Gaze and M. J. Keating. Pp 105-193. (British Medical Bulletin Vol. 30, No. 2.) (British Council: London, May 1974.) UK £2.25; elsewhere £2.50.

THE title of this bulletin is most appropriate for the two thirds concerned with studies on the nervous systems of animals. Research on nerve specificity and regeneration using histology, electron microscopy, surgery and electrophysiology is described. The rest of the bulletin is concerned with medical and social topics to which the physiological studies should be relevant: the epidemiology of spina bifida, the effect of malnutrition on intelligence, the educability of the subnormal. Though the gap between the two groups is to some extent bridged by Balács's description of metabolic influences on brain development in both animals and men, the difference in treatment is marked. This is inevitable as long as the relation between nervous connections and learning is unknown. Only Cragg speculates on this, discussing his work on synaptic patterns in mentally deficient mice.

The physiological articles are mostly excellent reviews of areas of research. Gaze's article on neuronal specificity in goldfish is particularly lucid. I found the other articles slightly less satisfactory, because of the relative paucity of facts. An exception is Bower's fascinating review on the innate abilities of newborn babies and how these develop. The bulletin is well presented and will be invaluable for those interested in the wide fields it covers.

GILLIAN MOORE

City life

Human Settlements: The Environmental Challenge. (A Compendium of United Nations Papers Prepared for the Stockholm Conference on the Human Environment, 1972.) Pp. xvi+209. (Macmillan: London and Basingstoke, March 1974.) £5.95.

Man, Materials, and Environment. National Academy of Sciences: National Academy of Engineering. Pp. xviii+236. (MIT: Cambridge, Massachusetts and London, 1973.) \$3.95.

Topophilia: A Study of Environmental Perception, Attitudes and Values. By Yi-Fu Tuan. Pp. x+260. (Prentice-Hall: Englewood Cliffs, New Jersey, January 1974.) \$8.95 cloth; \$4.95 paper.

THE United Nations Conference on the Human Environment held in Stockholm 1972 may well prove one of the most significant events of the decade. Consequently a volume of collected papers from the conference is likely to form a valuable reference to any research group working in this area. One feature of economic growth has been the enormously rapid development of cities, particularly in developing countries, and the fifteen background papers prepared on this issue around the theme "The Planning and Management of Human Settlements for Environmental Quality" are brought together in this work. The papers are not intended to be original. What they attempt to provide is a thorough and coordinated review and analysis of current problems in each subject area. Included are general commentaries on comprehensive development planning, population growth and distribution, rural development, a case study on the environmental impact of Polish industry on Warsaw central city, transport and communication, waste disposal and sewage and lastly, a relatively short account of social, cultural and aesthetic factors. An appendix lists those recommendations of the conference concerned with settlement and urbanisation.

The main purpose of *Human Settlements* is to demonstrate the importance of the careful planning and management of human settlements and that this should be recognised as a major means of assuring an appropriate environment for human survival and development. The book emphasises the point that pollution need be by no means an unavoidable consequence of economic development. The suggestions made in the various chapters (written by different authors although not individually named here) are wide ranging but suffer in that they tend to be over-generalised and lack a certain coherence of view; possibly inevitable in a set of collected papers. Nevertheless the work contains much of

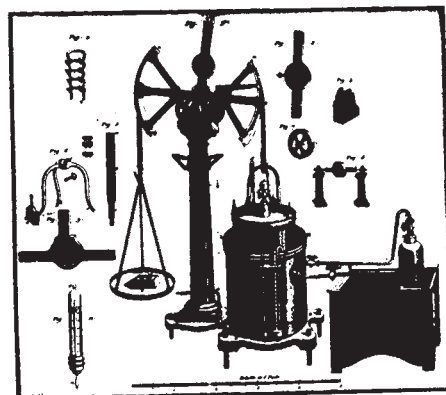
interest to those who would argue that it is in towns and cities, where most people spend the bulk of their lives, that the environment matters most. Two factors mitigate against wholeheartedly recommending it as a purchase for the individual researcher; the first is that two years have elapsed since the conference in June 1972; the second is an exceedingly high price for what, after all, is a summary.

By comparison, *Man, Materials and Environment*, a report on materials policy in the United States in relation to environment, has been produced with laudible rapidity. Using the formula of direct replication of authors' typescript has kept the cost down to a reasonable level and resulted in a book sturdy enough to withstand its presumably limited life (in this rapidly developing research area). The book represents the findings of a number of authoritative study groups contracted by the National Academy of Sciences, one of whose roles was to evaluate the effects on US materials policy of the suggestions of the Stockholm Conference. The aim of the study groups was to identify major issues and propose some positive actions with respect to public policy and research. The detailed findings of the teams are conveniently summarised in the first chapter. The second chapter, on the economic implications of seeking a high environmental quality, sets out the arguments for and against reduction in the overall rate of economic growth. The problems of metallic and non-metallic mineral extraction, fuels and forest products and the relations of domestic policy for international trade are tackled in turn and included for good measure is a comparative case study of environmental resource problems and policies in Japan. Particular attention is paid to the operation of the 'polluter pays' principle in a mixed economy and this method is advocated for the United States (and has now also been accepted by the European Commission for inclusion into the Community Environment Protection Programme). Emission taxes rather than subsidies are reckoned to be the socially least expensive but in a number of areas, such as packaging, the suggestion is that experimentation will lead to the best allocation of charges. In the main, this volume is entirely constructive, suggesting lines of research and policy methods to safeguard the future of the natural environment. One may jibe at some of the emphases but in doing so must accept that the research proposed will help to clarify these areas of uncertainty. A book certainly to be recommended to any serious researcher in this field.

Finally, Tuan's book *Topophilia*, easily compensates for the absence of

discussion about cultural aspects of the environment found in the other volumes. Topophilia is the affective bond between people and place. In this enjoyable and stimulating book Tuan sets himself the task of describing a complicated synthesis and he has succeeded admirably. The book has Tuan's distinctive style and communicates well both his subject and his own love of it. He approaches the questions: What are our views on the physical environment, natural and man made? How do we perceive, structure and evaluate it? What have been and what are our environmental ideals? How do economy, life style, and the physical setting affect environmental attitudes and values? What are the links between environment and world views? He traces and compares the answers to these questions from the early Greeks to the modern American city, the Aivilik Eskimo and the Hopi Indian, between humans and animals. By contrasting the perceptions and activities of man, the city dweller with that of his forbears, Tuan exposes both the richness and the poverty of city life. He builds an image of 'civilised' man's perception of nature, especially the 'countryside', as a reaction to the city which itself was originally evolved as an escape from the dangers of the wilderness. Thus, Tuan describes the city as a symbol, even tracing the history and function of city nicknames. For example, of the four American cities with the largest number of nicknames, New York (the Big Apple, the Babylonian Bedlam) boasts its world status, Washington its political supremacy, Chicago projects civility and San Francisco elegance. Of a different

Dispensing gases



Lavoisier's gasometer, taken from his *Traité élémentaire de Chimie*. The gasometer supplied a stream of gas flowing at a steady rate to a reaction chamber and was used in the demonstration of the quantitative composition of water; it was introduced to Holland by Martinus Van Marum. From *Martinus Van Marum: Life and Work*; vol. 4, Van Marum's Scientific Instruments in Teyler's Museum. By G. L'E. Turner and T. H. Leveres (Noordhoff: Leyden, 1973. Dfl. 60).

culture, Tuan describes how the rain-forest environment of the pygmy with its lack of horizon and landmarks, without pattern, has resulted in a world view in which the sense of distance and perspective is "distorted" and a sense of time is curtailed.

But to dip into the book, despite the inherent interest of every page, is not to do it justice because it must be emphasised that Tuan has composed a coherent and systematic thesis, analysing those innate aspects of our values and perceptions which we seem to share with other life forms, from those which mark us as individuals, or as members of a certain culture or subgroup. Possibly, and this might be taken as an anticipation rather than an omission from an otherwise comprehensive work, Yi-Fu Tuan's thesis could have led into a deeper discussion of the evolving nature and complexity of contemporary society in relation to concepts such as "post-industrial society" and "future shock", but perhaps this is for another volume. What he has achieved is to extend a way of looking at the natural and physical environment which demonstrates and calls for an appreciation of our own and other people's values and way of life at all levels of planning. The book is inexpensive and well indexed and should provide a useful and thought provoking basic text for both the casual reader and university courses dealing with urban geography, man in relation to the environment or the humanities.

H. S. D. COLE

Acoustic orientation

Echolocation in Animals. By E. S. Airapet'yants and A. I. Konstantinov. (Translated from Russian.) Pp. vi+309. (Academy of Sciences of the U.S.S.R. Joint Scientific Council on Physiology of Man and Animals.) (Israel Program of Scientific Translations: Jerusalem; Wiley: Chichester; January 1974.) £10.50.

THIS book was first published in the Soviet Union in 1970. It reviews Russian literature up to 1969 and Western literature up to 1968 so that many important discoveries made within the past five years are not covered. The major part of the book is devoted to studies on bats. This includes sections on the biology of bats, the nature of sound waves and methods of studying bat sounds. The signals emitted by bats are described and methods of sound production and radiation are discussed. Studies on both the auditory system of bats and their echo location ability are dealt with in some detail. Echo location in birds and small mammals is also discussed, but very briefly. The chapters on Cetacea include descriptions of their biology, mechanisms

of sound production and reception, a review of the different signals emitted by these animals and a consideration of their echo location performance. The final chapter of the book is devoted to echo location in pinnipeds.

The main value of the book is that it draws together much recent Russian literature on echo location. Russian work is described in some detail, particularly in the sections on hearing in bats and on the echo location abilities of both bats and dolphins. Although this is useful for non-Russian readers, it often results in considerable imbalance in the treatment of different topics; a more comprehensive treatment of some topics would have been useful. For example, the authors describe their own equipment to illustrate methods of studying bat signals. But this excludes a consideration of equipment used by other workers, such as portable bat detectors and sound spectrographs, both of which are important in the study of bat signals. Displays from the latter, taken from the literature, are presented later in the book with no explanation and occasionally without adequate labelling.

The authors express the hope that the book will appeal to readers of many professions, but very little help is given to interdisciplinary readers or to newcomers to the subject. For instance the theoretical considerations of various aspects of echo location are often difficult to follow and many of the equations are given without any hint of derivation or a source reference. Also, descriptions of the anatomy of the larynx and the auditory pathways are given as a string of latin names, without adequate explanations or diagrams. The absence of an index is also a great drawback and makes the book difficult to use as a reference text.

On the whole the English translation from the Russian is very readable but there is some awkwardness of expression in which the exact meaning is often not clear. Some apparently literal translations have been given, for example 'humeral girdle' and 'cathode repeater' when these could have been fairly easily replaced by their more commonly accepted equivalents, here 'pectoral girdle' and 'cathode follower' respectively.

Some points of production are irksome. The latin names of species and genera are not italicised (this is a reversal from the Russian text) and the references given in the text and in the bibliography are not always accurate or consistent.

Because the literature on echo location is expanding so rapidly, a new comprehensive, critical review would be welcome. This book is disappointing both in the treatment of the material and in its presentation and does not

fulfil the requirements of such a review. But because of its account of Russian work, the book will be a useful, though expensive, addition to literature on bioacoustics.

GILLIAN D. SALES

Plant ecology in Africa

East African Vegetation. By E.M. Lind and M. E. S. Morrison. Pp. xvii+257. (Longman: London, April 1974.) £6.

THE appearance of this work will be hailed by those interested in tropical Africa as an ecological milestone, for in spite of excellent herbaria and taxonomic works, biologists have had to work in these regions without the aid of a general description of the vegetation. Indeed in many cases, large mammal research schemes have been devised without reference to botanical studies.

The authors have avoided the difficulties of describing vegetation with long lists of plant names by referring to dominant species and community structure, and relating this information to details of microclimate, water relations, soils and productivity. Additionally, they have succeeded in relating botanical information to simple descriptions of animal communities.

Vegetation types are dealt with in considerable detail and include forest habitats, rangelands (grassland and wooded grassland), inland aquatic vegetation, coastal vegetation (including intertidal and mangrove swamps), and high altitude vegetation. Considering the difficulties of describing local conditions existing at altitudes ranging from sea level to 19,000 foot, the authors have achieved a good balance between purely descriptive material and broader ecological information.

Part two discusses the influence of water availability and temperature on plant form, structure and growth followed by a short chapter on soils: the description of catenary soil associations and their vegetation types is particularly valuable.

Alan Hamilton contributes a useful chapter on vegetational history, in which he examines evidence derived from macro fossils, pollen analysis and plant geography. Of particular interest is the author's comparison of the apparently impoverished African forests with those of Malaysia and South America. He concludes that the flora of these areas have been depauperated at a time when the climate was very dry.

This valuable addition to the tropical literature will be of great value to research workers, teachers and students at all levels, and with luck will provide a new impetus for field botanical studies in Africa.

MALCOLM COE

Hormones to kill insects

Insect Hormones and Bioanalogues. By K. Sláma, M. Romanuk and F. Sorm. Pp. ix+447. (Springer-Verlag, Vienna and New York, 1974.) \$45.90.

WITH its various sections written by an insect physiologist and by two organic chemists, this is primarily a chemical study of two groups of insect hormones, the juvenile hormone and the moulting hormone (ecdysone), and of the numerous synthetic materials with similar physiological activities. The natural juvenile hormone in the body of the insect they call consistently the corpus allatum hormone (CAH) and all isolated chemicals, whether natural or synthetic, which show the same activities in greater or less degree, they call 'juvenoids'. Likewise the natural moulting hormone in the body is named the prothoracic gland hormone (PGH) and all natural and synthetic chemicals with the same activities they call 'ecdysoids'. This is a useful convention which avoids much unnecessary argument.

The chemical structure and the various syntheses devised for natural juvenoids and ecdysoids are described in great detail with clear and consistent structural formulae throughout, and at the end of the book a table of some 350 compounds gives structural formulae and the approximate dosage required for equivalent activities of each, in a range of a dozen or so insects which have been extensively used for assay purposes; and a further table gives an alphabetical list of the same 'juvenoids' according to their chemical derivation. Sorm and Romanuk have worked extensively in this field of organic chemistry in relation to both juvenoids and ecdysoids, and the book contains much previously unpublished information from their laboratory. But published work from elsewhere is well covered; although doubtless much more information remains in the hands of commercial firms which have been active in this field.

The table of activities provides a useful basis for reflections and speculations about the chemical factors concerned in the relative activity of juvenoids—but the figures must, of course, be interpreted with caution, since a 15-fold increase in activity of a given compound may result if it is applied to the cuticle at a dilution of 1:1,000 or more in a non-volatile oil, as compared with the usual method of application in a volatile solvent (such as acetone or octane) which leaves an undiluted residue of the active principle on the surface. And a similar increase in activity results if the application is spread in the form of small doses throughout the sensitive period in the

life of the insect, as compared with a single application at the outset.

The authors are principally concerned with the possibility of juvenoids (and to a less extent of ecdysoids) being used as insecticides: to render insects non-viable by disturbance of their normal metamorphosis; to arouse dormant insects from diapause at some inclement season of the year; to sterilise females by adverse effects on their developing ovaries; or to produce non-viable embryos or teratological injuries to young larvae by applications to pregnant females or to newly laid eggs. As a background for such considerations Sláma provides a very full review of the normal hormonal physiology of insects and of the effects of ecdysoids and juvenoids.

The endocrinology of insects is beset with numerous pseudo-problems. What are the chemical effects of ecdysoids? Do they induce DNA synthesis, or RNA synthesis? When renewed growth results in cell multiplication (as it commonly does) DNA synthesis of course occurs; but if sufficient cells already exist it has long been known that moulting (with or without metamorphic change) can take place without DNA synthesis. Renewed growth commonly means renewed protein synthesis; it has long been known that within an hour or so of ecdysoid treatment RNA is increasing in the affected cells—but the same happens in many other cells without the need of ecdysoids. An early effect of ecdysoids at metamorphosis in some caterpillars is conversion of tryptophane into red ommochrome pigments; in fly larvae, the conversion of tyrosine into quinones to sclerotise the puparium. But all such effects are episodes in the growth process which ecdysoids initiate; they are not direct effects of the hormone. The juvenile hormone was originally described as 'inhibiting' metamorphosis; and that is a fair enough description. Unfortunately this was interpreted to mean an antagonistic relation between this hormone and the moulting hormone; an idea which has led to much unprofitable controversy. The earliest suggestion on the nature of the 'inhibitory action' of the juvenile hormone was that it accelerated the deposition of the new cuticle and thus arrested 'differentiation toward the adult form'. This process was clearly demonstrable; but many years elapsed before it was realised that it is due to excessive amounts or precocious timing of moulting hormone supply and not to the juvenile hormone. Finally, it is often very difficult to distinguish between direct effects of a hormone and feedback or homeostatic effects resulting from its action elsewhere in the body. By and large Sláma adopts the rational view in dealing with these

problems; but he gives a conscientious account of much of the literature, which tends to obscure the rationality of his approach.

V. B. WIGGLESWORTH

Liquid physics

Liquid State Physics: A Statistical Mechanical Introduction. By Clive A. Croxton. Pp. x+421. (Cambridge University: London, May 1974.) £10.

DR CROXTON'S intention in writing this book was to provide a guide to the uninitiated. On the whole, I think he has achieved this aim, although the book is not in any sense an elementary one. The material covered in the first chapter deals with the theory of imperfect gases and forms a sound basis for the latter sections. The method of correlation functions is introduced in the second chapter and is applied to the problems of the liquid state in the way associated with the names of Kirkwood, Rice, Percus and others. Chapters 3 and 5 aim to discuss the numerical side of the subject and to make a comparison between theory on the one hand and experiment or computer simulation on the other. Here the difficulty that faces all authors in writing textbooks on subjects which are developing rather rapidly is that some of the material necessarily is out of date even before the book is published. There are statements which doubtless Dr Croxton would now wish to modify in the light of recent work.

Chapter four is, to my mind, the most worthwhile in the book. The nature of the surface of liquids has been sadly neglected in the past both from an experimental and a theoretical point of view. Dr Croxton brings the special properties of the surface into the context of distribution functions and contact is made between theory and measurement by special reference to the surface tension. This is a field in which the author himself has made a major contribution and this fact is reflected in the clarity with which difficult ideas are explained. The chapter concludes with a short but very useful exposition of the way that the basic theory must be modified to handle surface properties of quantum liquids.

The final chapter is concerned with transport processes, and this is a subject which has been covered quite adequately in the past in a number of review articles. There is perhaps room for a little more comparison between the neutron diffraction work and theory, but this is compensated by the very comprehensive list of up-to-date references which the author attaches to the chapter.

J. E. ENDERBY

Weapons and laws of war

The Problem of Chemical and Biological Warfare. Vol 2: CB Weapons Today; vol. 3: CBW and the Law of War. Stockholm International Peace Research Institute. Vol 2: Pp. 420; vol. 3: pp. 194. (A study of the Historical, Technical, Military, Legal and Political Aspects of CBW, and Possible Disarmament Measures.) (Almqvist and Wiksell: Stockholm; Humanities: New York; Elek: London, 1973.) Vol. 2: Sw.kr.75; \$16.50; £7.50; vol. 3: Sw.kr. 40; \$10; £5.

THESE two latest volumes in the SIPRI series maintain the scholarly distinction and absorbing interest of their predecessors (volumes 1, 4 and 5, published in 1971, were reviewed in *Nature*, 236, 355; 1972.) Volume 2 now takes the historical survey of CB Weapons, defences, policies and programmes beyond 1945 where volume 1 left off. It brings together in a masterly way the available information on contemporary CBW technology and examines as far as is known the policies of each state towards the use of CBW, including tables indicating continent by continent states' formal attitude towards the 1925 Geneva Protocol and the 1972 Convention on Biological and Toxin Weapons, which is not yet in force.

This volume, written by Julian Perry Robinson, with the assistance of Carl-Göran Hedén and Hans von Schreeb, is essentially a work of information, endowed with more than 1,600 references in addition to footnotes. Special attention is paid, as one would expect in a SIPRI publication, to the importance of research and development programmes and the relationships thus engendered between the military and scientific communities (pages 325–332). Specific R and D programmes, such as that concerned with 'binaries', are also described.

Volume 3, written by the Danish peace researcher Anders Boserup, addresses itself to the question: what does international law, and specifically the international law of war, have to say about CBW? One might think this a straightforward question, the answer to which could scarcely deserve a volume to itself: a question in any case less interesting than whether the law is 'strong' enough, and if not what can be done to strengthen it, subjects on which SIPRI had already had much to say in volume 5. One might therefore expect volume 3, being "only concerned with the legal issues in the narrow positivist sense of determining what the law says" (page 42), to be uncontroversial to the point of boredom.

Not so. For there happens to be considerable disagreement over the state of the law. Most of the responsibility for the present uncertainty must

be laid at the door of those governments which have made it their business to discover and exploit supposed ambiguities in the Versailles Treaty formula for defining chemical weapons. This 1919 formula—"asphyxiating, poisonous or other gases and all analogous liquids, materials or devices"—was also embodied in the Washington Treaty of 1922, which did not enter into force, and the Geneva Protocol of 1925, which did. More than 90 states are now parties to the protocol.

What is agreed is that there exists a legal prohibition on the use of chemical weapons and biological methods of warfare. But is the chemical ban as absolute as the biological? Is the content of the prohibition in customary international law more extensive than the treaty prohibition binding only parties to the Geneva Protocol? Is retaliatory use of CBW as firmly banned as first use? And what is the legal effect of the reservations made by many states, including Britain, upon ratifying the protocol, reserving the right to employ CBW against not only the state which violates the protocol but equally against that state's allies?

The SIPRI study examines these and other questions but deals most fully with two matters of bitter controversy: harassing agents (gases such as CN and CS) and chemical herbicides. The controversy is first resolved, systematically, into four questions: (1) Is the use in war of harassing agents prohibited, on condition of reciprocity, among parties to the Geneva Protocol? (2) Is the use in war of herbicides likewise prohibited under the protocol? (3) Is the use in war of harassing agents prohibited nowadays by a peremptory norm (*jus cogens*) of customary international law, binding (by definition) on all states irrespective of their attitude to the protocol? (4) Is the use in war of herbicides likewise prohibited by a peremptory norm?

SIPRI's treatment of these four key questions is thorough, well informed and tightly argued. In the end we find that the answer given to each of the four is yes, although it is admitted (pages 137–8) that (4), the customary prohibition of herbicides, is less conclusively proved than the first three. This is partly because *jus cogens* is a vague concept, with no such precise apparatus of proof as the rules of treaty interpretation provide; partly because evidence of state practice and belief is relatively slender.

So SIPRI settles for the most extensive view of the state of the law, incidentally supporting U Thant and the United Nations General Assembly in the views which they separately expressed in 1969 and from which few states other than the United States

have ever deviated. Some of the restrictive interpretations suggested seem to have been based on misunderstandings or ignorance of international law, whereas of others the kindest thing that can be said is that they "can only arise from a highly specious reading of the Protocol" (page 43). Both comments apply in full measure to the notorious British policy statement purporting to exclude CS gas from the scope of the protocol: a policy as legally untenable (and unnecessary) now as when it was first announced in 1970. SIPRI once again condemns the British statement (pages 59–62) but, as in previous volumes of this study, attributes it to improbable causes, overlooking the clues contained in its very ineptitude of expression.

In conclusion this volume can be warmly commended, but with two qualifications. Its author did not have time to take adequate account of the implications of states' signature and ratification of the 1972 convention. Indeed, the reference (page 149) to this partial disarmament treaty is marred by a faulty argument regarding the significance of the withdrawal clause which assumes, mistakenly, that use of BW and toxins was among the activities banned by the convention. (It should have been; but on that point Britain was obliged, by Sweden and the East European states, to give way in the autumn 1971 round of negotiations, so that the Convention ended up with no ban on use as such). Less excusable on grounds of time is the failure (pages 62–3) to distinguish between interpretations of the Geneva Protocol and statements of intent for future CW agreements. The 1970–71 policy declarations of Canada, Norway and the Netherlands were clearly of the second type and should not have been adduced as evidence supporting the extensive interpretation of the protocol.

N. A. SIMS

Geochemistry handbook

Handbook of Geochemistry Vol. 2/3. K. H. Wedepohl (executive editor) and C. W. Correns, D. M. Shaw, K. K. Turekian and J. Zemann (editorial board). Pp. iv+845. (Springer-Verlag: Berlin and New York, 1974.) DM 258; \$99.40.

THE *Handbook of Geochemistry* has been taken a further substantial step towards completion with the publication of this section. Chapters for sixteen new elements are introduced; of these only that for barium is supplied in entirety, although substantial parts of the chapters on nitrogen, fluorine, gallium, selenium, indium, tellurium and thallium are also provided. Eleven

other sections relate to incomplete chapters which have already been published and these allow the completion of another nine chapters (lithium, sodium, potassium, zinc, rubidium, cadmium, cesium, platinum and bismuth). Now that more than half the text, in both number of elements and pages, is complete (chapters for more than fifty elements are now complete, or virtually so), much of the frustration caused by gaps is removed. The standard of production remains high.

D. G. MURCHISON

Putting viruses together

Morphogenesis of T-Even Bacteriophages. By B. F. Poglazov. Pp. vi+105. Monographs in Developmental Biology, Vol. 7. (Karger: Basel, London and New York, 1973.) 54 Sw.fr.; £7.85; \$16.75.

In a monograph which might better be entitled "T4 structural proteins and their assembly", the author has attempted to integrate the extensive physical and chemical studies on the proteins of bacteriophage T2 from his laboratory with the genetic analysis of phage development which has come out of laboratories in Europe and the United States in the past ten years. The product is a review of the results of roughly 100 papers arranged according to the part of the phage structure whose assembly is being considered.

Of the seven chapters, the two principal ones are devoted to assembly of the head and tail of T4 and T2. The discussion of head morphogenesis is devoted to the inferences on form determination which can be drawn from genetic analyses of mutants in T4 head genes and the interesting experiments from Poglazov's own laboratory on structure formation from solubilised phage T2 head protein. Unfortunately, little mention is made of the work which has been published to elucidate the role of DNA in phage head formation, a subject of considerable recent controversy.

The assembly of the phage tail receives the longest treatment—fully half the book. Again most space is devoted to the work of Poglazov and his collaborators on dissociation and reassociation of tail tube and sheath protein.

A short and extremely dense chapter is devoted to tail fibre assembly. The brevity is unfortunate because the fibre assembly pathway is certainly the best example of a morphogenetic pathway in T4 assembly, and beautifully illustrates the complementary approaches of genetics, immunology, electron microscopy and biochemistry to problems of structure formation. But enough references are given to

enable the interested reader to fill in the details for himself.

In his devotion to detail, Poglazov obscures some of the larger problems of phage morphogenesis. There is hardly any mention of the timing of phage development, regulation of quantities of various components synthesised, or of possible mechanisms of length or form determination.

Generally, the author's policy is to present observations and results without comment. The lack of synthesis will make for difficult reading for the uninitiated, and the lack of evaluation of published results will at times be misleading for those not already familiar with the difficulties of experimentation in the field.

MICHAEL K. SHOWE

Weather satellites

Climatology from Satellites. By E. C. Barrett. Pp. xii+418. (London Methuen: London, May 1974.) £7.90.

THE idea of this book, if I have divined its origins aright, is to live up to the teaching of climatology in schools—and, perhaps, to geographers in universities—by introducing the subject through the medium of satellite pictures, backed up by the analysis of other kinds of satellite data. Or it may be meant just to give a fresh view of the subject in this way. The 41 satellite photographs are the book's main attraction. Among the more impressive ones are several which show the frontal cloudsheets of the northern and southern hemispheres trailing till they meet in the equatorial convergence and one (plate 19), a half-month composite, which shows the cloudless zone along the equator in the Pacific extending from the Americas as far as 170°E. It is a pity that the minimum brightness composite (plate 9) which gives a sample of the rendering of ice and snow and persistent cloud was chosen from the Antarctic summer.

The book is written for geographers; others may find it useful as a handy small guide to the early history of weather satellites, the data and issues which are now available, the symbols in common use on map analyses of satellite information and so on. Among its features are a table (on page 21) of the spatial resolution and frequency of various kinds of satellite observation, the list of routinely available average, minimum and maximum brightness maps and their uses (on pages 50-51), the long table (pages 87-92) on identification of cloud types from satellite photographs, the samples of infrared techniques for deriving surface and cloud-top temperatures, mean cloudiness and relative humidities and the

introduction (on pages 111-7) to the derivation of precipitation from satellite surveys. More could have been said about the inadequacy of precipitation measurements at the surface, with the insoluble problems of representative catchment of the precipitation at sea and of snowfall anywhere, and the potential virtue of uniformity in derivations, however difficult and indirect, from satellite observations. We learn (page 124) that most cloud bands in all latitudes are aligned with the surface wind; we learn also, however, the complications and limited possibilities of accuracy in deriving wind speeds and cloud-top heights.

But whether climatology can be taught in the way this book attempts it may be doubted. The effect is rather like that of walking into a cinema in the middle of the film: the order of presentation is strangely jumbled. We meet the gradient wind on pages 120-3, the sun as the source of energy on page 147 and are rewarded for patience with a nice set of pole-to-pole profile diagrams of the various components of the energy budget on page 159.

I hope not to be unfair in saying that I found this author's style foreign and difficult; for example the ambiguous statement on page 71 that: "the amplitudes and locations of the maxima and minima of incoming radiation are seasonally variable" (within a given season? from season to season? or when we compare the same season in different years?). The waves in the upper westerly winds are introduced (page 196) with the statement that they "undulate meridionally". The stratospheric circulation is explained (page 209), only too briefly, as "a huge standing wave related to the zone of maximum insolation": in this the book clearly attempts too much. Finally, the odd statement is made that an atlas of cloudiness might seem uninteresting except in relation to programmes of space research and Earth Resources Technology Satellites, though we are persuaded that the knowledge is needed for computer modelling and for tracing the general circulation of the atmosphere: surely the last named is the average viewer's first exciting impression of satellite cloud photography.

The author is an enthusiast for the use of satellite observations and has contributed valuable studies of the circulation and cloud development over the tropics, which occupy much of the regional climatology section of the book. Despite the irritating awkwardnesses, the book succeeds in communicating this enthusiasm and may therefore succeed also in stimulating the general reader to try out the use of this fascinating tool himself and seek further understanding. H. H. LAMB

Group theory

Classical Groups for Physicists. By Brian G. Wybourne. Pp. xvi+415. (Wiley: New York and London 1974.) £10.60.

THIS is a fine introduction to the group theoretical method in modern physics. During the past twenty-five years, the significance of symmetry transformations in describing physical phenomena has come to be recognised more and more and with it the use of group theory—and particularly the theory of Lie groups, due to the work of Wigner, Racah and others. This volume gives an exposition of Lie group theory for physicists following the traditional treatment of Weyl and Cartan as modified by the work of Dynkin and the Russian School.

The book divides into two major parts. The first presents a detailed exposition of the principal features of Lie groups and algebras and their topological structures, leading up to the Cartan-Weyl classification. Diagrammatic techniques of Dynkin are used to construct simple Lie algebras, and concepts of weights, Casimir invariants, and Clebsch-Gordon coefficients are discussed in detail. The discussion is mostly carried through for compact groups though there is a brief section on the non-compact $SU(1, 1)$. This portion of the book is written very much from a physicist's point of view—that is to say, principal concepts are introduced, results stated though not always proved with the emphasis being very much on ideas and the methodology rather than on rigour. I thoroughly approve of the approach—I only wish this part of the book was longer.

The second part treats the group theory of three topics in detail—the isotropic harmonic oscillator, the hydrogen atom and the shell structure in nuclear theory. There is an excellent bibliography.

I would recommend the book for postgraduate students in nuclear theory and high energy physics as a self-contained introduction to the advanced ideas and techniques.

ABDUS SALAM

Intelligent beings

The Development of Mind. By A. J. P. Kenny, H. C. Longuet-Higgins, J. R. Lucas and C. D. Waddington. Pp. 152. (Gifford Lectures 1972/1973.) (Edinburgh University: Edinburgh, April 1974.) £2.25.

THE traditional Gifford Lecture, with some notable person putting forward a synthesis of his views on natural theology, is a well established part of the British intellectual scene. For two recent winters, however, something

different has been tried: a group of four people have shared the lectures, and at each session one person gave an opening statement, and there was then discussion between the four. Although each man is widely talented, they could be labelled as specialists in artificial intelligence, philosophy, theology, and biology respectively: and this volume reports the second series of such lectures.

On the whole, the title is taken as referring to the appearance of minds in the course of evolution: not in the other possible sense of the development of a mind from that of the baby to that of the Gifford Lecturer. There are some cursory references to the latter problem, but on the whole the assumption is taken that "there is overwhelming evidence that our most primitive skills . . . are inborn". The discussion concentrates mostly therefore on the view of the world we ought to have if evolution has given rise to creatures possessing our capacities: problems in fact not too dissimilar from those handled by Monod in *Chance and Necessity*, and that book is mentioned several times. By contrast with a book like Monod's, one naturally does not get a unified and single point of view in all its complexity: the main merit of this kind of attack is rather that any overemphasis by one lecturer can instantly be picked up by another. Thus for example the argument that language is difficult to explain by natural selection, because it is only of benefit when more than one person has it, is immediately countered by the argument that we only have to explain a series of small steps in improving communication, rather than the sudden appearance of a complete complex syntax. For those who want the balance and interaction of the various points of view represented, this will in some ways be a more satisfying book than that of Monod. Probably one should not lay down that all future Gifford Lectures should be of this type: but it was worth the attempt on this occasion.

Reaction to lectures on natural theology is bound to be a personal matter: but in two ways this volume fails to speak to my condition. First, the emphasis is on the processes which produce mind and not upon its nature, and this is linked with a silent assumption that all human beings have the kind of minds which can be heard discussing in Oxford and Edinburgh common rooms. Yet the outburst of studies of the behaviour of the developing child, and for that matter of adults with a rather different type of mind from the academic one, make one a bit doubtful of the generality of this kind of discussion. Our ancestors looked at the species which now exist

and could see no way to explain the other than by special creation: and there is something of the same flavour about these discussions which take the mind as an unanalysed given, without considering development within the individual. To psychologists therefore, whose professional blinkers forbid them to take for granted what the mind is and what it does, this kind of discussion is bound to seem curiously old fashioned and irrelevant.

This kind of reaction leads on to another at a more human level. The pressing problems of natural theology seem to some psychologists to lie, not in the origin of species including ourselves, but in the problems which a human being may face in achieving a stable and satisfactory way of organising his mind, in the existence of alternative ways of doing so, in the need to change from one way to another as circumstances change, and in the difficulties in doing so once some mode of reaction has been established in an earlier situation. In the older, and doubtless outworn, language, these are the problems of the consciousness of sin and the experience of redemption, rather than those of the creation of the world, and perhaps they might be regarded as outside the field of the Gifford Lectures. They can, however, be the subject of rational discussion, quite apart from the particular solutions offered to them, and some of us would like to read a similar volume on that line even more than this one.

DONALD E. BROADBENT

Where sediments build up

Depositional Sedimentary Environments, with Reference to Terrigenous Clastics. By H. E. Reineck and I. B. Singh. Pp. xvi+439. (Springer-Verlag: Berlin and New York, 1973.) DM108; \$44.30.

IN recent years there has been a spate of books published in the field of sedimentary geology. These have included general texts on the origin and petrography of sedimentary rocks and processes of sedimentation, and many dealing with specific sedimentary environments. The authors of this volume are to be congratulated on compiling and analysing all the major modern sedimentary environments in which terrigenous clastic sediments are deposited. The potential scope of the subject is so vast, yet the authors have succeeded in summarising it in a most readable manner. To this end, most of the information can otherwise only be seen in journals, so the book should provide both professional geologists and students with a commendable review of depositional environments.

The first part of the book deals

Second skin



Sloughing palmate gecko from the Nambi desert in south-west Africa. From *The World of Reptiles and Amphibians* by Maurice Burton, (Orbis: London, February 1974.) £2.50.

specifically with primary sedimentary structures and textures, commencing with a brief summary of the major hydrodynamic factors controlling the formation of certain types of structure. This section is similar in its approach to other monographs on the subject. One of its assets is that, as well as being descriptive, the authors have attempted to summarise the varied opinions on the genesis of sedimentary structures. It is perhaps unfortunate that more attention was not paid to the hydrodynamic significance of sedimentary structures, and that the importance of chemical and mineralogical parameters should have been restricted to just over two pages. Also, this section does get involved at times with rather laborious classification schemes.

In the second and most important part of the book the emphasis is placed on modern environments and includes an encyclopaedic treatment of glacial, desert, lake, fluvial, delatic, coastal, shelf and lagoon, tidal flat and ocean basin environments. The authors have, where possible, based their discussions on studies published within the last decade. Consequently, the book provides an up to date, and at times stimulating, appraisal of the subject. Certain topics have been treated to greater depths than others, due in part to a combination of the particular expertise of the authors and a current lack of detailed knowledge on some modern environments. But, in all chapters, the writers have been objective in their efforts to present the processes and characteristic structures and sequences typifying given sedimentological regimes. A pleasing feature is that, from the choice of examples, it is clearly demonstrated that more than one facies model is often required for a particular environment. Furthermore, the importance and application of biological parameters is stressed throughout.

The book is lavishly illustrated with

579 diagrams and photographs, mostly of high quality, but often rather repetitive. It is in fact a little irritating at times to find, due to their large number, that many of the figures are out of phase by several pages with the text. Editorial standards are high, and both printers' and geological errors are at a minimum. The reference list is most comprehensive and should prove to be invaluable for literature searches.

BRIAN WAUGH

Stellar surface

Cosmic Gas Dynamics. By Evry Schatzman and Ludwig Bierman. Pp. xv+291. (Wiley: Chichester, March 1974.) £8.40.

PROBLEMS of gas dynamics are of importance in most branches of theoretical astrophysics, and a comprehensive treatise on cosmic gas dynamics would be vast indeed. A glance at this volume immediately indicates its specialised nature in spite of its general title. Roughly two thirds of the book is taken up by Schatzman's article on stellar hydrodynamics. The remainder is devoted to a study of the physics and dynamics of the solar wind written by Biermann. There is no attempt to link the two articles and they can be read independently of one another.

Schatzman's article is concerned largely with hydrodynamic and hydro-magnetic phenomena occurring in the outer layers of main sequence stars. Stars of spectral types A to G possess extensive outer zones in which the energy transport is largely by convection. The properties of convection zones are not well understood, and their structure is generally described by the phenomenological approach of mixing length theory. The convective motions act as a source of pressure waves which may propagate outwards into the surrounding radiative zone. The study of these waves and their effects are of great

importance in establishing the properties of the stellar corona. A large section of the article deals with these problems. Various aspects of stellar surface activity, such as solar flares, are discussed and the article ends with a brief discussion of the possible role of stellar mass loss in the angular momentum decrease which must occur as stars contract onto the main sequence. Although well written, the article makes few concessions to the reader, and a fairly good background of hydrodynamics and magnetohydrodynamics is necessary to follow the discussion.

The existence of the solar wind is a direct consequence of the types of subsurface stellar phenomena referred to earlier. Biermann first briefly reviews the properties of the solar corona, and then describes in more detail the gross dynamics of the corona and solar wind. A logical progress from simple inviscid hydrodynamics to two-temperature models is followed. The conditions under which the flow may be described by macroscopic equations are discussed and reference is made to solar wind models in which the ion properties are approached by way of the Vlasov equation. The interplanetary magnetic field and the angular momentum of the wind are briefly treated, and the article ends with a short discussion of the interface of the wind and interstellar medium. I was rather disappointed to find no account of the interaction of the wind with planetary bodies and comets.

Both authors are well known for their extensive contributions to the work they describe and write with considerable authority. I have two criticisms. The diagrams have been taken directly from the literature without any attempt to relate their size to the amount of information contained in them. The caption arrangements are very poor. Captions are separate from the figures in some cases, two figures are captioned merely as "universally familiar", and one caption is in French. The second criticism is the very long delay between the writing of the articles and the publication date. The contents are based on lectures given by the authors in 1968 with slight amendments made in 1970. This delay has been particularly unfortunate for the otherwise excellent article by Biermann. Since the time of writing, satellite observations have given a great deal of information directly bearing on the subjects in the article. Considerable progress has been made theoretically and the extensive reviews in the *Asilomar Conference Proceedings* are available in print. The publication delay has not affected the stellar hydrodynamics section as much, but then £8.40 is a great deal to pay for 176 pages of lecture notes. J. E. DYSON

obituary

Vannevar Bush

Dr Vannevar Bush died on June 28 at his home in Belmont, Massachusetts. He was 84. He had been Professor, Vice-President and Dean of Engineering at the Massachusetts Institute of Technology in the 1920s and 1930s, and President of the Carnegie Institution in Washington, DC, from 1939 to 1955. While there, he served as science adviser to President Roosevelt. He was Chairman of the Corporation of MIT from 1957 to 1959 and Honorary Chairman from 1959 to 1966.

Bush received BSc and MSc degrees from Tufts College in 1913. With money for only one year's study, he entered MIT and earned a doctorate in electrical engineering in that single year. In 1916, the DEng was awarded to him jointly by MIT and Harvard.

After the entry of the United States into the First World War he did anti-submarine research, developing a magnetic device for detecting submarines. In 1919 he returned to MIT as associate professor of power transmission.

In studies of power lines, he found that traditional mathematical methods were inadequate for the analysis of increasingly complex systems. In 1925 he set several graduate students to work designing an analogue machine called the Product Integrator to grapple with such problems. It was the first in a series of machines which were precursors to modern computers.

His Differential Analyser was completed in 1931 and was so successful that it served as a prototype for machines built elsewhere in Europe and the United States. This led to the construction of a 100-ton giant known as the Rockefeller Differential Analyser, which had 2,000 tubes, 200 miles of wire and 150 motors.

In 1939 he began meeting with a small group to discuss what might be done to prepare for a massive technological programme which was thought to be essential if the United States entered the war. They concluded that the nation was "... pathetically unprepared from the standpoint of new weapons".

In early 1940, Dr Bush went to President Roosevelt with the group's plan for the establishment of the National Defense Research Committee. The President approved, and appointed Dr Bush as its chairman. Compton took charge of radar research, Conant chemistry and explosives. Jewett com-



Dr Bush with the differential analyser (Courtesy: MIT).

munications and Tolman armour and ordnance. Research activity became so extensive that by 1941 the Office of Scientific Research and Development was established, with Dr Bush as director.

In 1941, after preliminary studies indicated the feasibility of developing an atomic bomb, Dr Bush secured the President's approval to proceed and gave Dr Conant the responsibility for the programme. When the project was ready for large-scale construction, it was turned over to the Corps of Engineers, which established the Manhattan Engineering District to carry the enterprise to completion. A Military Policy Committee, to function as a kind of board of directors, was formed, with Bush as chairman and Conant as his deputy. Following the death of President Roosevelt, it was Dr Bush who gave the first detailed information about the bomb to President Truman. Bush, Conant and Compton were members of the Interim Committee which, after careful deliberation, recommended to the President that the bomb be used.

Of that recommendation, Dr Bush wrote in *Pieces of the Action*: "I knew that Japan would succumb within a matter of months even if the bomb were not used. But I also knew that an invasion of Japan was already being mounted, that it involved several hundred thousands of estimated casualties, and that once rolling, it could not be stopped in its tracks. I also felt that use of the bomb, far less terrible in my mind than the fire raids on Tokyo, if it brought a quick end to the war, would save more Japanese lives than it snuffed out.

"But there was another aspect of this heavy subject. By that time I knew that civilisation faced an utterly new era

and I felt that it might as well face it squarely. I knew that nerve gases delivered in a dozen different ways, could be as terrible as an A-bomb. And I had no illusions about the potential power of biological warfare. When science became really applied to warfare, which occurred only during the Second World War, it presented humanity with two alternatives. Either it could refrain, formally or informally, from use of weapons of mass destruction—no only the bomb but also gases and bacteria and viruses—or it could thrust itself back into the dark ages. Over twenty years have passed, and the world has understood and has thus far refrained. If for no other reason I would justify the use of the bomb at Hiroshima and Nagasaki because it was the only way in which the dilemma could be presented with adequate impact on world consciousness."

At the same time he was responding to Roosevelt's request for a comprehensive report on postwar scientific research policy. Published in 1945 under the title *Science the Endless Frontier*, it contained the recommendations of committees (which Dr Bush had organised) to make studies, with respect to health, education, unemployment and other areas in which science would play a part. Dr Bush wrote: "... without scientific progress no amount of achievement in other directions can insure our health, prosperity and security as a nation in the modern world ... Basic scientific research is scientific capital. Moreover, we cannot any longer depend upon Europe as a major source of this scientific capital."

The report was a stimulus for growth in science and technology with an impact on virtually every aspect of American life. The National Science Foundation was established as a major source of Federal support for research. The Office of Naval Research was formed to move far beyond the limits of traditional military research. When the Department of Defense was organised Dr Bush became chairman of its Research and Development Board.

A justifying typewriter was one among a number of Dr Bush's inventions. While still at MIT he invented a high speed library research machine called the rapid selector which was taken over by the Navy for cryptanalysis. He obtained his first patent in 1912 while he was still in college, for a machine mounted on two bicycle wheels which could be used in surveying land. He was granted dozens of patents and built many unpatented devices, ranging from a birdfeeder which discriminated against pigeons and bluejays to hydrofoil boats.

Endless Horizons and *Modern Arms and Free Men* were two of Dr Bush's popular books.